Estimating Workplace Air and Worker Blood Lead Concentration using an Updated Physiologically-based Pharmacokinetic (PBPK) Model

October 2013

Air, Community and Environmental Research Branch

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

Estimating Workplace Air and Worker Blood Lead Concentration using an Updated Physiologically-based Pharmacokinetic (PBPK) Model

October 2013

Office of Environmental Health Hazard Assessment (OEHHA)

California Environmental Protection Agency

Authors

Kathleen Vork, Ph.D., Research Scientist
Jim Carlisle, D.V.M., M.Sc., Staff Toxicologist
Joseph P. Brown, Ph.D., Staff Toxicologist

Air, Community and Environmental Research Branch

OEHHA Scientific Reviewers

Robert Blaisdell, Ph.D., Chief (Retired), Exposure Modeling Section, Air Toxicology and Epidemiology Branch

Melanie Marty, Ph.D.
Assistant Deputy Director for Scientific Affairs

Andrew G. Salmon, M.A., D.Phil., Chief, Air Toxicology and Risk Assessment Section, Air, Community and Environmental Research Branch

David Siegel, Ph.D., Chief,
Air, Community and Environmental Research Branch

Lauren Zeise, Ph.D.
Deputy Director for Scientific Affairs

George Alexeeff, Ph.D., Director

Allan Hirsch, Chief Deputy Director

External Scientific Reviewers

Earlier versions of this document were reviewed by five independent peer reviewers selected for their expertise in the fields of toxicology, occupational medicine, industrial hygiene, mathematics, pharmacokinetics, and physiologically-based pharmacokinetic (PBPK) modeling. Their invaluable expertise contributed to the development of the final document. The peer reviewers are listed below.

John R. Froines, Ph.D., University of California, Los Angeles, Department of Environmental Health Sciences, Los Angeles, CA

Gary L. Ginsberg, Ph.D., University of Connecticut, School of Community Medicine, Farmington, CT

Dale B. Hattis, Ph.D., Clark University, The George Perkins Marsh Institute, Worcester, MA

Michael J. Kosnett, M.D., M.P.H., University of Colorado, Department of Medicine and Department of Environmental and Occupational Health, Denver, CO

Richard W. Leggett, Ph.D., Oak Ridge National Laboratory, Environmental Sciences Division, Oak Ridge, TN

Table of Contents

Summary 1

1 Introduction 5

2 Methods and Results 6

2.1 Selection and modification of lead model 6

2.2 Predicting blood lead from workplace air and vice versa (Task 1) 7

2.2.1 Model adjustments and assumptions 7

2.2.2 Inhalation transfer coefficient 8

2.2.3 Validation of the Leggett+ Model 9

2.2.4 Simulating Workers' Blood Lead using Leggett+ 10

2.3 Time to decline to target BLL following removal from workplace exposure (Task 2) 13

2.3.1 Scenario one: Constant PbA resulting in identified blood lead levels 14

2.3.2 Scenario two: Declining workplace air concentrations sustaining over 40 years a BLL reached in one year 18

3 Discussion 19

3.1 Updates to approach taken by Center for Policy Alternatives to predict air lead/blood lead relationships 20

3.2 Limitations and uncertainty 21

3.2.1 Population BLL variability 21

3.2.2 Breathing rate 22

3.2.3 Erythrocyte saturation 22

3.2.4 Lead's toxic effects could alter the kinetics of lead in the body 23

3.2.5 Particle size distribution 23

3.2.6 Gastrointestinal absorption 25

3.2.7 Lead in bone 25

4 Summary and Conclusions 25

A Appendix: Review, Selection, Modification, and Testing of Lead Models 27

A.1 Lead biokinetics 27

A.1.1 Pulmonary deposition and clearance 27

A.1.2 Gastrointestinal absorption 28

A.1.3 Erythrocyte uptake and saturation 29

A.1.4 Uptake and elimination from blood and soft tissue 29

A.1.5 Uptake and elimination from bone 29

A.2 Model screening 30

A.2.1 Bert model 32

A.2.2 Leggett model 33

A.2.3 O'Flaherty model 37

A.3 Model selection 40

A.4 Further evaluation and adjustment of the nonlinear Leggett model 42

A.4.1 Coding integrity 42

A.4.2 Assessing model performance 44

A.5 Conclusion 65

B Appendix: OEHHA Modifications to the Adjusted core Model to Accommodate Workplace Exposure in Leggett+ Model 67

B.1 Description of exposure features added to the nonlinear Leggett model 67

B.1.1 Breathing rate 67

B.1.2 Inhalation transfer coefficient 68

B.2 Methods for deriving a coefficient for the transfer of inhaled lead to blood in workers 71
B.2.1 Studies selected for analysis 71
B.2.2 Lead particle dosimetry using the MPPD2 model 72
B.3 Results 74
B.3.1 Dosimetry results from MPPD2 74
B.3.2 Dosimetry results from ICRP Human Lung Model publication 66 lookup tables 80
B.3.3 Default inhalation transfer coefficient (ITC) 82
B.4 Methods for assessing the performance of the Leggett+ model 85
B.4.1 Study and subject selection criteria 86
B.4.2 Data extraction 87
B.5 Results 90
B.5.1 Test 1: Goodness of fit 92
B.5.2 Test 2: Model performance versus exposure duration 94
B.6 Conclusion 95
C Appendix: Acronyms, symbols and special terms 97
D References 99

Tables

1: Parameters employed in OEHHA's application of the Leggett+ model 11
2: PbA concentrations and corresponding BLL 12
3a: Workplace air lead concentration (PbA) (µg/m3) for different durations of exposure corresponding to the BLL reached 14
3b: Days for BLL to decline to 15 µg/dL after removal from workplace exposure (limit BLL reached at the end of exposure period) 15
A-1: Parameter values from Nie and Leggett and adjusted core model 56
A-2: Estimate of fit of predicted to observed BLLs for 47 smelter workers 57
A-3: Distribution of Lead in Various Tissues - Postmortem Data, Original Model Prediction, Adjusted Model Prediction 64
B-1: Airborne lead concentration and particle mass median aerodynamic diameter from Park and Paik (2002) 74
B-2: Lung dosimetry analysis of occupational airborne lead exposure by the MPPD2 model: multiple activity levels 76
B-3: Lung dosimetry analysis of occupational airborne lead exposure by the MPPD2 model with different speciation assumptions (data of Park and Paik 2002; Spear et al. 1998a) 78
B-4: Lung dosimetry analysis of occupational airborne lead exposure in brass foundry workers by the MPPD2 model (data of Liu et al. 1996) 80
B-5: Particle deposition by activity level and particle size by the ICRP Human Lung Model (ICRP 1994) 81
B-6a: Inhalation transfer coefficient by worker group and activity level 84
B-6b: TWA inhalation transfer coefficients by occupational setting 84
B-7: Model inputs 90
B-8: Measured BLL versus BLL predicted by Leggett+ 91

Figures

1: Rise in BLL over 40 years in the 95th percentile worker 13
2: Modeled skeletal and blood lead levels for the median worker during and after workplace exposure (Leggett+ model) 17
3: Modeled skeletal and blood lead levels for the median worker during and after workplace exposure (Leggett+ model) 18
A-1: Measured versus predicted BLL (adjusted nonlinear Leggett model) 59
A-2: Model performance versus job tenure 60
A-3: Plasma lead versus whole blood lead concentration - predictions from the adjusted Leggett model and data from two worker cohorts 62
A-4: Urine lead versus whole blood lead concentration - predictions from the adjusted Leggett model and data from two worker cohorts 62
B-1: Model validation diagram 86
B-2: Check for systematic bias – Griffin et al. 1975 93
B-3: Check for systematic bias – Williams et al. 1969 94
B-4: Model performance versus exposure duration – Griffin et al. 1975 95

Summary

This document presents the results of a modeling effort by the California Environmental Protection Agency's (Cal/EPA) Office of Environmental Health Hazard Assessment (OEHHA) to estimate air and blood lead concentrations among workers under various exposure conditions. These estimates are intended to accompany proposed changes to workplace standards for lead exposure developed by the California Department of Public Health's Occupational Lead Poisoning Prevention Program (CDPH-OLPPP). This work was performed under contract with the CDPH-OLPPP.

The principal tasks requested of OEHHA were to:

1. Estimate various concentrations of lead in workplace air inhaled by workers without respiratory protection that could result in specified lead concentrations in workers' blood.
2. Estimate the time it would take for workers' blood lead levels to return to 15 µg/dL (micrograms of lead per deciliter of blood) following the cessation of occupational lead exposure.

Because there are no chamber or field studies that include measurements of air lead levels and blood lead levels (BLLs) over the time span of interest (40-year working lifetime), some type of model must be used to predict the relationship between lead exposure and BLL. The model must reflect the complexity of lead absorption, distribution, metabolism, and excretion, and be able to address time-dependent conditions.

OEHHA reviewed the available lead pharmacokinetic models and selected the Leggett model (nonlinear version) as best suited to complete the required tasks. To the extent possible, OEHHA calibrated the model to fit observed data and tested the validity of the adjusted model. Briefly, OEHHA simultaneously adjusted blood, bone, and urine clearance parameters in the core model to fit blood, bone, and urine data collected from workers chronically exposed to lead, as well as the general population environmentally exposed to lead. We then performed multiple tests to ensure that predictions from the

adjusted model in the range of BLLs of interest to CDPH-OLPPP compared well to observed data. Once confident that the adjusted core Leggett model predicted valid BLLs, OEHHA used the model to complete the required tasks. The results are presented below.

Task 1: Blood Lead Levels Resulting from Lead in Workplace Air

OEHHA added exposure features and adjustments to the core nonlinear biokinetic model for lead published by Richard W. Leggett in 1993. We added the exposure model to the adjusted core model (resulting model called Leggett+) so that we could simulate workplace inhalation exposure that would predict a range of workers' BLLs after 40 years of occupational exposure and a given background ambient air and dietary exposure. The original Leggett model was a general model not specifically designed to address workplace exposure scenarios. Therefore, OEHHA needed to add exposure features which addressed breathing rate (BR) and the fraction of inhaled lead transferred to blood ("inhalation transfer coefficient" or "ITC") under workplace exposure conditions. OEHHA derived an ITC based on published particle size distribution data from a variety of workplaces and a recently developed model for predicting upper and lower respiratory tract deposition based on particle size and other parameters.

The results of this modeling are expressed as 8-hr time-weighted average workplace air lead concentrations (PbA) (in micrograms of lead per cubic meter of air [$\mu g/m^3$]) and corresponding BLLs (in units of µg/dL) in a median worker. Using population BLL distributions based on epidemiologic data, we calculated BLLs for workers at the 90th and 95th percentiles of the population, as shown in Table S-1.

Table S-1: Workplace air lead concentrations (PbA) and corresponding BLL[1]

8-hr TWA PbA (µg/m^3)	Predicted BLL (µg/dL)		
	50th percentile	90th percentile	95th percentile
0.5	2.3	4	**5**
0.8	2.7	**5**	6
2.1	4.6	8	**10**
2.4	**5**	9	11
2.8	5.5	**10**	12
3.9	6.9	13	**15**
5.0	8.2	**15**	18
6.0	9.3	17	**20**
6.5	**10**	18	22
7.5	11	**20**	24
10.4	14	25	**30**
11.5	**15**	27	32
12.6	16	**30**	35
17.6	**20**	37	43
25.0	25	46	54
34.0	**30**	55	65

[1] Assumptions as in Table 1; TWA, time-weighted average workplace air concentration given ambient and oral background intake leading to a BLL of 1.5 µg/dL; PbA, workplace air lead concentrations (in micrograms of lead per cubic meter of air [µg/m^3]); BLL, blood lead level; BLL values that CDPH-OLPPP asked OEHHA to model are in **bold;** GSD, geometric standard deviation used to derive 90th and 95th percentile estimates = 1.6. See Table 1. No measure of variability was given by (Leggett 1993) or (O'Flaherty 1993), (O'Flaherty et al. 1998), O'Flaherty (2000)**.**

Task 2: Time Taken to Restore Blood Lead to 15 µg/dL

Using the adjusted core Leggett model, OEHHA evaluated the time required for workers' BLLs to decline from a much higher BLL to 15 µg/dL following cessation of 1, 10, 25, or 40 years of workplace lead exposure. CDPH-OLPPP asked that we model the decline of BLLs from limits of 20, 30, 40, 50, and 60 µg/dL to some lower BLL. We used a target of 15 µg/dL because the CDPH-OLPPP Medical Guidelines recommend that a worker with an elevated BLL not return to work until his or her BLL is below 15 µg/dL (CDPH 2009).

OEHHA considered two different scenarios for modeling time to decline. In the first scenario, workers are exposed to constant airborne lead concentrations during work hours, resulting in BLLs of 20, 30, 40, 50 or 60 µg/dL at the end of each exposure

period. The results for scenario one are presented in Table S-2. Note the substantial (about five-fold) difference in the time it takes to decline to 15 µg/dL after 40 years of exposure reaching a BLL of 60 µg/dL compared to a BLL reaching 30 µg/dL, due to a greater rate of lead accumulation in the bones at the higher BLL. In the second scenario, workers are exposed to constant PbA during work hours, resulting in BLLs of 20, 30, 40, 50, or 60 µg/dL within the first year. During the balance of the exposure period, the assumed workplace air concentrations decrease gradually so that BLLs are sustained at the level reached within the first year. Scenario one and two result in similar times to decline to 15 µg/dL for all BLLs and all exposure periods.

Table S-2: Days for BLL to decline to 15 µg/dL after removal from workplace exposure (limit BLL reached at the end of exposure period)[1]

Exposure duration	Percentile	BLL at beginning of MRP[1] (µg/dL)				
		20	30	40	50	60
		Days to decline to 15 µg/dL				
1 year	50th	21	128	280	435	615
	90th	38	234	511	795	1123
	95th	45	277	605	940	1329
10 years	50th	31	200	400	630	920
	90th	57	365	731	1151	1681
	95th	67	432	865	1362	1989
25 years	50th	32	207	416	670	1005
	90th	58	378	760	1224	1836
	95th	69	447	899	1448	2172
40 years	50th	32	210	425	685	1045
	90th	58	384	776	1251	1909
	95th	69	454	919	1481	2259

[1] Medical Removal Protection – Under Cal/OSHA regulations whenever an employee's BLL exceeds specified limits he or she must be removed from high lead exposure until his or her BLL returns to an acceptable level; µg/dL, micrograms per deciliter; Limit BLL reached exposure at the end of the exposure period. GSD, geometric standard deviation used to derive 90th and 95th percentile estimates = 1.6. See Table 1. No measure of variability was given by (Leggett 1993) or (O'Flaherty 1993), (O'Flaherty et al. 1998), O'Flaherty (2000).

1 Introduction

The California Department of Public Health's Occupational Lead Poisoning Prevention Program (CDPH-OLPPP) is in the process of recommending changes to the Cal/OSHA standards relating to workplace exposures to lead. CDPH-OLPPP contracted with the California Environmental Protection Agency's (Cal/EPA) Office of Environmental Health Hazard Assessment (OEHHA) to provide physiologically-based pharmacokinetic (PBPK) modeling to support that effort. The support consists primarily of two tasks using PBPK modeling to predict:

1. the ranges of concentrations of inorganic lead in workplace air in micrograms per cubic meter (µg/m^3) that would result in blood lead levels (BLLs) of interest (5, 10, 15, 20, and 30 micrograms per deciliter [µg/dL]) for the 50th, 90th, and 95th percentile of workers exposed to lead by inhalation.
2. the rate of BLL decline to 15 µg/dL - the level proposed by CDPH-OLPPP - following cessation of occupational lead exposure that resulted in BLLs in a range from 20 to 60 µg/dL with exposure histories from 1 to 40 years.

Completion of these tasks will supply important information supporting the consideration of a revised lead standard: Task 1 model predictions of the air concentrations resulting in certain BLLs will inform the choice of a health-based permissible exposure limit (PEL) intended to ensure that BLLs in workers would stay below a level proposed by CDPH-OLPPP. Task 2 supports the prediction of the length of time overexposed workers will have to be kept away from workplace exposure in order for their BLL to return to 15 µg/dL.

This document begins with a description of OEHHA's methods for selecting and modifying the lead model, predicting blood lead, analyzing the time for BLLs to return to 15 µg/dL from a range of higher BLLs. It is followed by a discussion of the ways OEHHA has updated the model and the limitations and uncertainties that remain. The final Section summarizes OEHHA's work and its concluding statements. Appendix A covers the review, selection, modification, and testing of the candidate model for predicting blood levels from workplace exposure to lead. Appendix B reports the procedures for

deriving an exposure module and adding it to the adjusted core model to accommodate workplace exposure conditions. This appendix then (Leggett+) reports the procedures for checking accuracy of the combined model, Leggett+. Finally, Appendix C defines acronyms that appear throughout this report.

2 Methods and Results

2.1 Selection and modification of lead model

In order to complete the two above-mentioned tasks, OEHHA evaluated the available models to determine which model best describes what is known about the complex pharmacokinetics of lead and could be most easily modified to estimate worker exposure. The results of this review are summarized below. A detailed comparison and evaluation of these multi-compartmental biokinetic models, including a summary of each model's conceptual structure, advantages, and limitations, is in Appendix A. OEHHA reviewed the following models:

- Leggett (1993) model
- O'Flaherty (1993), (1995); O'Flaherty et al. (1998); O'Flaherty (2000) model
- Bert et al. (1989) model

The U.S. Environmental Protection Agency's Adult Lead Model (U.S. EPA 2003) is a steady-state model that is unable to accommodate the time-dependent requirements of the above tasks, and was eliminated from further consideration. The All-Ages Lead Model (U.S. EPA 2005), based on the Leggett model, was also considered for this project. However, it had not been released in final form at the time of this report and was therefore not considered further.

As discussed in Appendix A, OEHHA found the Leggett model to be the best suited for use in an occupational lead exposure scenario because it:

- is sufficiently flexible to allow modeling of the required scenarios.
- has an optional algorithm allowing for nonlinear kinetics to account for red blood cell saturation at higher BLLs.

- provides a good fit to data from humans exposed to environmental lead and limited data from lead workers.

Dr. Leggett coded his published model in FORTRAN (**For**mula **Tran**slating System*)*, which is an old computer language. Our preferred platform for PBPK modeling is Matrix Laboratory™ (MATLAB) (MATLAB 2012). Therefore, OEHHA coded the Leggett model into script language used by MATLAB. We then compared the output from the original and nonlinear models recoded in MATLAB with the output generated by the author (personal communication with Dr. Leggett, 2011) to ensure that the coding was accurate.

2.2 Predicting blood lead from workplace air and vice versa (Task 1)

To support the development of a new PEL, OEHHA used the Leggett model (nonlinear version) with added exposure features to predict workplace airborne lead concentrations that would lead to BLLs of interest to CDPH-OLPPP following various simulated 40-year workplace exposures.

2.2.1 Model adjustments and assumptions

In preparation for these tasks, OEHHA modified the Leggett model by: 1) adjusting bone, urine clearance, and blood parameters to improve the fit of the model to observed data; 2) assuming a time-weighted average breathing rate of 26 m^3/day, which reflects time-weighted breathing rates based on assumed activity levels for workplace and non-workplace exposure to airborne lead; and 3) setting a default value of 30% for transfer of inhaled lead to blood ("inhalation transfer coefficient") for particles in the size range found in industrial settings. We named the modified version of the Leggett model "Leggett+", to distinguish between the original model and the version OEHHA modified. These new features are described in detail and tested in Appendices A and B. We describe the derivation of the ITC briefly here because it introduces a new approach to estimating the transfer of inhaled lead to blood from exposures in the workplace.

2.2.2 Inhalation transfer coefficient

For any given air lead concentration, the proportion of inhaled particles that deposits in the head, ciliated regions of the lung, and alveoli is determined by the size of the particles and the individual's breathing rate. Generally, smaller particles will deposit deeper in the lung while coarser particles tend to be deposited in the head and ciliated regions where they are cleared by ciliary action or secretions and swallowed. Very small particles will to a large extent be exhaled.

The chemical form of the inhaled lead affects its solubility and therefore influences absorption from the respiratory tract and gut. For purposes of developing a coefficient for the transfer of inhaled lead to blood, OEHHA chose to make the cautious assumption that lead is inhaled in a highly soluble form and that inhaled lead particles deposited in the alveolar region of the lung are absorbed to the blood within a day with essentially 100% efficiency. Particles deposited in the head and ciliated regions of the lung are cleared to the gut where they are absorbed with less efficiency.

Particle size distribution has been considered a significant influence on the percentage of inhaled lead transferred to the blood although, as will be shown later, the fraction ultimately transferred to the blood does not vary greatly by particle size distribution in the range 1 – 15 µm mass median aerodynamic diameter (MMAD). This is because the decrease in the fraction deposited deep in the lung when particle sizes are large is offset by an increase in the total head deposition fraction (larger particles are not exhaled but deposit in the head region) and subsequent swallowing and gut absorption.

In order to determine what default value to use for the percentage of inhaled lead transferred to the blood we: 1) reviewed published literature on particle size distribution in a variety of industrial workplaces with differing lead operations that generate a range of particle sizes (fine to coarse) and extracted particle MMADs; 2) estimated the proportion of inhaled lead particles that deposits in the head, ciliated regions of the lung, and the alveoli, using the reported MMADs and the Multi-path Particle Dosimetry version 2 model (MPPD2) (ARA 2012); and 3) derived a transfer factor according to Equation 1:

Eq. (1): Inhalation transfer = (alveolar deposition x lung absorption) + (ciliated and head region deposition x average gut absorption).

We calculated inhalation transfer coefficients for four different industrial settings (two that generate finer particles and two that generate coarser particles) and five activity levels (resting, sitting, light work, moderate work, heavy work). We selected 30% as our default inhalation transfer coefficient (ITC) after analyzing the data in three different ways. We calculated:

1) an ITC for each occupational setting assuming an average BR of 25 L/min during the exposure period (range 30.1% - 30.5%).
2) ITCs for all four occupational settings and all five activity levels (range 28% - 32%, midpoint 30%).
3) a time-weighted average (TWA) transfer coefficient for each occupational setting using the same activity weighting factors we used to derive a 24-hr average breathing rate (range 29% - 31%; midpoint 30%).

The reader is referred to Appendix B for a full discussion of the rationale and assumptions used for deriving the default value.

Validation of the Leggett+ Model

As mentioned previously, OEHHA adjusted the bone, urine clearance, and blood parameters in the Leggett model to improve the model fit to observed worker data. We performed multiple tests of the model to ensure that predictions in the range of BLLs of interest to CDPH-OLPPP from the adjusted model compared well to tissue lead levels measured in workers and the general population. We were able to verify that the adjusted Leggett model predicted BLLs after chronic exposures very close to measured BLLs; the model performed well regardless of job tenure; predicted levels of lead in blood, urine, and bone compared well to measured levels in chronically-exposed workers; and predicted levels of lead in all tissues compared well to measured levels in the general population.

Once OEHHA was comfortable that the core model described above was performing well, we added an exposure component (BR and ITC) to the core model so that we

could model workplace exposures based on personal breathing zone lead concentration. To test its performance, we used Leggett+ to reproduce (to the extent possible) exposure scenarios in a published field study and a chamber study, and compared model predictions to measured BLLs from each study. These comparisons show that, in the range of BLLs of interest to CDPH-OLPPP, the Leggett+ model predicts BLLs similar to observed BLLs in these studies (see Appendix B).

2.2.3 Simulating Workers' Blood Lead using Leggett+

The simulations in this report assumed a standard background BLL of 1.5 µg/dL based on the background levels observed in the U.S. general population (Schober et al. 2006). This BLL represents constant exposure to an ambient air level of 0.006 µg/m^3 (the 2004 annual average level in California [SCAQMD 2008]), along with 14.6 µg/day of background oral intake from all non-work sourcesor a combined uptake of 1.8 µg/day (see Table 1). There is uncertainty in estimating individual background intake, but the background constitutes a small fraction of total exposure for most lead workers. Inputs and assumptions used in simulating the specific exposure scenarios requested by CDPH-OLPPP are shown in Table 1.

Table 1: Parameters employed in OEHHA's application of the Leggett+ model[1]

Parameter definition	Units	Value	Reference
Age at start of exposure	years	25	Based on retirement at age 65
Exposure duration	years	40	high-end assumption
Initial blood lead concentration	µg/dL	1.5	(CDC 2009; Schober 2006)
Workplace airborne lead concentration (PbA)	$\mu g/m^3$	0.5 - 210	back calculated (Tables 2 & 3a)
Transfer fraction of inhaled lead to blood	unitless	0.30	(see Appendix B)
Breathing rate[2]	m^3/day	26	(see Appendix B)
Background lead intake after absorption	µg/day	1.8	Back-calculated to maintain BLL at 1.5 µg/dL
Yearly exposure fraction	days/year	250/365	(U.S. EPA 1991)
Body weight	kg	73	(ICRP 2002)
BLL geometric standard deviation (GSD) in U.S. population.	unitless	1.6	(U.S. EPA 2011: Griffin et al. 1999)

[1] dL, deciliter; m^3, cubic meter; µg, microgram, kg, kilogram;[2] Breathing rates for sedentary, light, and moderate activity are weighted by work and non-work time in a day and by the yearly exposure fraction. A more detailed description of our assumptions appears in the Appendices and below under the section entitled: Limitations and Uncertainty (see text).

We used the Leggett+ model and the parameters listed in Table 1 to estimate the constant air concentrations that yield BLLs in the range of 2 – 30 µg/dL for the 50th percentile worker after 40 years of workplace exposure. We calculated the 90th and 95th percentile BLLs from the 50th percentile BLLs using Equations 2 and 3 - the standard statistical formulas for determining percentiles of a lognormal distribution.

Eq. (2): BLL (50th percentile) = BLL (95th percentile) / GSD $^{1.64}$

Eq. (3): BLL (90th percentile) = BLL (50th percentile) x GSD $^{1.282}$

The results are presented in Table 2.

Table 2: Workplace air lead concentrations (PbA) and corresponding BLL[1]

8-hr TWA PbA (µg/m^3)	Predicted BLL (µg/dL)		
	50th percentile	90th percentile	95th percentile
0.5	2.3	4	**5**
0.8	2.7	**5**	6
2.1	4.6	8	**10**
2.4	**5**	9	11
2.8	5.5	**10**	12
3.9	6.9	13	**15**
5.0	8.2	**15**	18
6.0	9.3	17	**20**
6.5	**10**	18	22
7.5	11	**20**	24
10.4	14	25	**30**
11.5	**15**	27	32
12.6	16	**30**	35
17.6	**20**	37	43
25.0	25	46	54
34.0	**30**	55	65

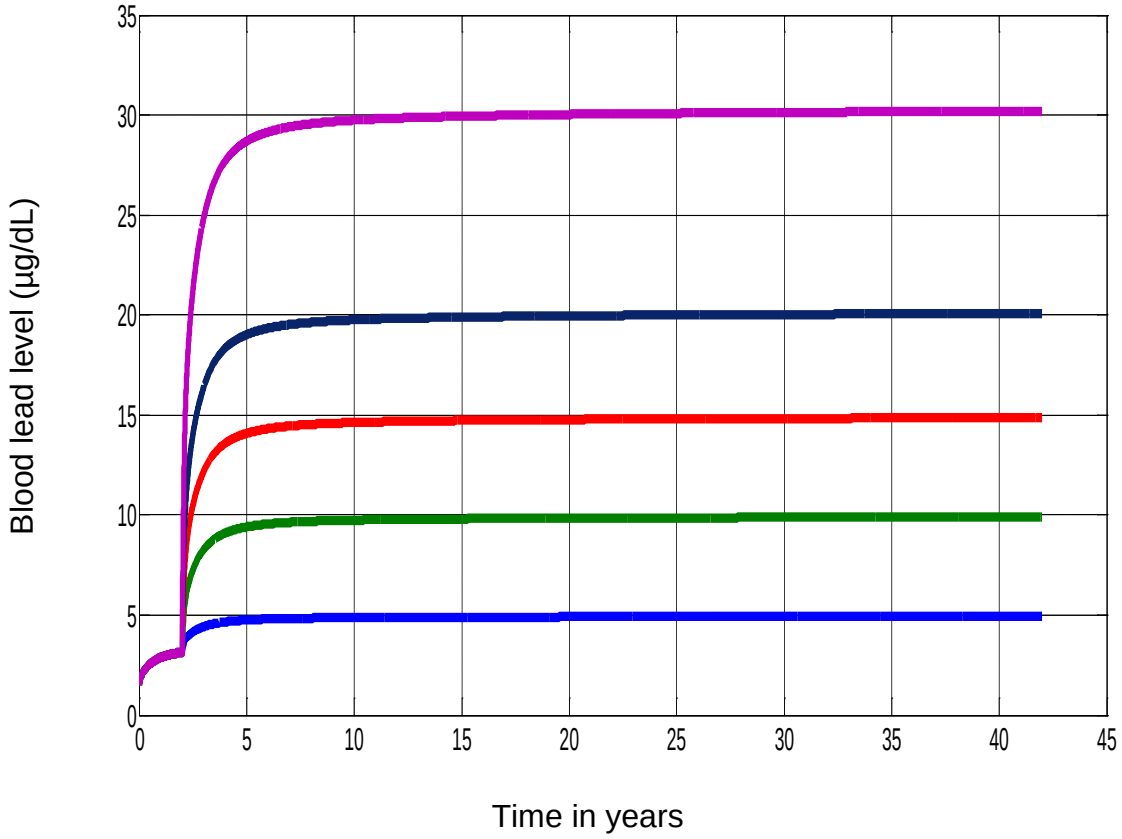
[1] BLL, blood lead level; µg/dL, microgram per cubic deciliter; assumptions as in Table 1; 8-hr TWA, eight hour time-weighted average workplace air concentration given ambient and oral background intake leading to a BLL of 1.5 µg/dL; workplace air lead concentrations (PbA) (in micrograms of lead per cubic meter of air [µg/m^3]); BLL, blood lead level; BLL values that CDPH-OLPPP asked OEHHA to model are in **bold.**

To obtain the 90th and 95th percentile BLLs, we assumed that individual variability in BLL in the U.S. general population is lognormally distributed with a GSD of 1.6. A GSD of 1.6 in the U.S. general population is suggested by Griffin et al. (1999) and has been adopted by the U.S. EPA (2011). However, before selecting a GSD of 1.6, OEHHA verified that it reasonably represents the variability in BLLs in studies of children, adult volunteers, and workers (for a description of our analysis, see section 3.2.1 Population BLL variability). As described previously, we applied the GSD to the 50th percentile BLL to derive the 90th and 95th percentile BLLs.

Figure 1 depicts the rise in BLL in the 95th percentile worker who reaches the limit BLL gradually over 40 years of workplace exposure. After achieving a stable background BLL with two years of exposure to background (non-workplace) sources of lead alone,

workplace PbA is added to background lead for 40 years. Note that BLLs climb rapidly during the first year of workplace exposure and continue to climb at a slower rate over the next two years and a very slow rate for the remaining years of exposure.

Figure 1: Rise in BLL over 40 years in the 95th percentile worker [1]



[1] BLL, blood lead level; corresponding 8-hr TWA air lead concentrations for BLLs of 5, 10, 15, 20, and 30 µg/dL are 0.5, 2.1, 3.9, 6.0, and 10.4 µg/m^3 respectively.

2.3 Time to decline to target BLL following removal from workplace exposure (Task 2)

Under the current Cal/OSHA-required medical removal protection program (MRP), whenever an employee's BLL exceeds specified limits he or she must be removed from high lead exposure work areas until his or her BLL returns to an acceptable level. Using the adjusted core model (Leggett+ without the exposure module), OEHHA simulated the time it may take to decline to a lower BLL for a range of elevated BLLs and exposure histories of interest to CDPH-OLPPP. OEHHA considered two different scenarios for

modeling time to decline. In the first scenario, workers reach the BLL limit at the end of the exposure period. In the second scenario, workers reach the BLL limit within the first year of exposure and the BLL limit is maintained for the remainder of the exposure period.

2.3.1 Scenario one: Constant PbA resulting in identified BLLs

OEHHA used Leggett+ to estimate the constant 8-hr TWA air concentration that would result in BLLs of 20, 30, 40, 50, and 60 µg/dL (referred to as "limit BLLs") at the end of the exposure period (Table 3a). Daily exposure was then reduced to background level at the end of the exposure period, and the time needed for each BLL to decline to 15 µg/dL was predicted (Table 3b).

Table 3a: Workplace air lead concentration (PbA) (µg/m^3) for different durations of exposure corresponding to the BLL reached[1]

BLL (µg/dL) reached	Exposure Period			
	1 year	10 years	25 years	40 years
20	23	18	18	18
30	44	35	34	34
40	75	60	60	59
50	125	101	100	100
60	210	169	166	166

[1]PbA, workplace air lead concentrations; BLL, blood lead level predicted by the model for the 50th percentile worker; µg/dL, microgram per deciliter

The workplace air concentrations found in Table 3a are within the range of air concentrations measured in lead-related industrial and construction workplaces (Hodgkins et al. 1992; Liu et al. 1996; Virji et al. 2009; Vork 2003).

At the end of each exposure period, the absorbed daily dose was reduced to the background level that sustained a BLL of 1.5 µg/dL, and the time needed for each BLL to decline to 15 µg/dL was predicted. The days needed to decline to 15 µg/dL for the 50th, 90th, and 95th percentile worker for each of five exposure periods appear in Table 3b. For example, 166 µg/m^3 of workplace air concentration together with background

levels of ambient air and oral sources of lead over 40 years produced a BLL of 60 µg/dL (Table 3a column 5). It took an average of 1045 days for the BLL to return to 15 µg/dL for the median worker (Table 3b column 7). We estimated the 90th and 95th percentiles from 50th percentile BLLs using Equations 2 and 3 - the standard statistical formulas for determining percentiles of a lognormal distribution.

Table 3b: Days for BLL to decline to 15 µg/dL after removal from workplace exposure (limit BLL reached at the end of exposure period)[1]

Exposure duration	Percentile	BLL at beginning of Medical Removal Protection (µg/dL)				
		20	**30**	**40**	**50**	**60**
		Days to decline to 15 µg/dL				
1 year	50th	21	128	280	435	615
	90th	38	234	511	795	1123
	95th	45	277	605	940	1329
10 years	50th	31	200	400	630	920
	90th	57	365	731	1151	1681
	95th	67	432	865	1362	1989
25 years	50th	32	207	416	670	1005
	90th	58	378	760	1224	1836
	95th	69	447	899	1448	2172
40 years	50th	32	210	425	685	1045
	90th	58	384	776	1251	1909
	95th	69	454	919	1481	2259

[1] Medical Removal Protection – Under Cal/OSHA regulations whenever an employee's BLL exceeds specified limits he or she must be removed from high lead exposure until his or her BLL returns to an acceptable level.; µg/dL, micrograms per deciliter; GSD, geometric standard deviation used to derived 90th and 95th percentile estimates = 1.6. See Table 1. OEHHA applied a standard statistical equation for a lognormal distribution of BLLs in the worker population because no measure of variability was given by (Leggett 1993) or (O'Flaherty 1993), (O'Flaherty et al. 1998), (O'Flaherty et al. 2000).

Note the substantial increase in the time it takes to decline to 15 µg/dL for higher limit BLLs. The time needed to decline to 15 µg/dL after 40 years of exposure reaching a BLL of 60 µg/dL (two half-lives) is about five times longer than the time needed to decline to 15 µg/dL after 40 years of exposure reaching a BLL of 30 µg/dL (one half-life). This striking difference is due to a greater proportion of lead accumulating in the

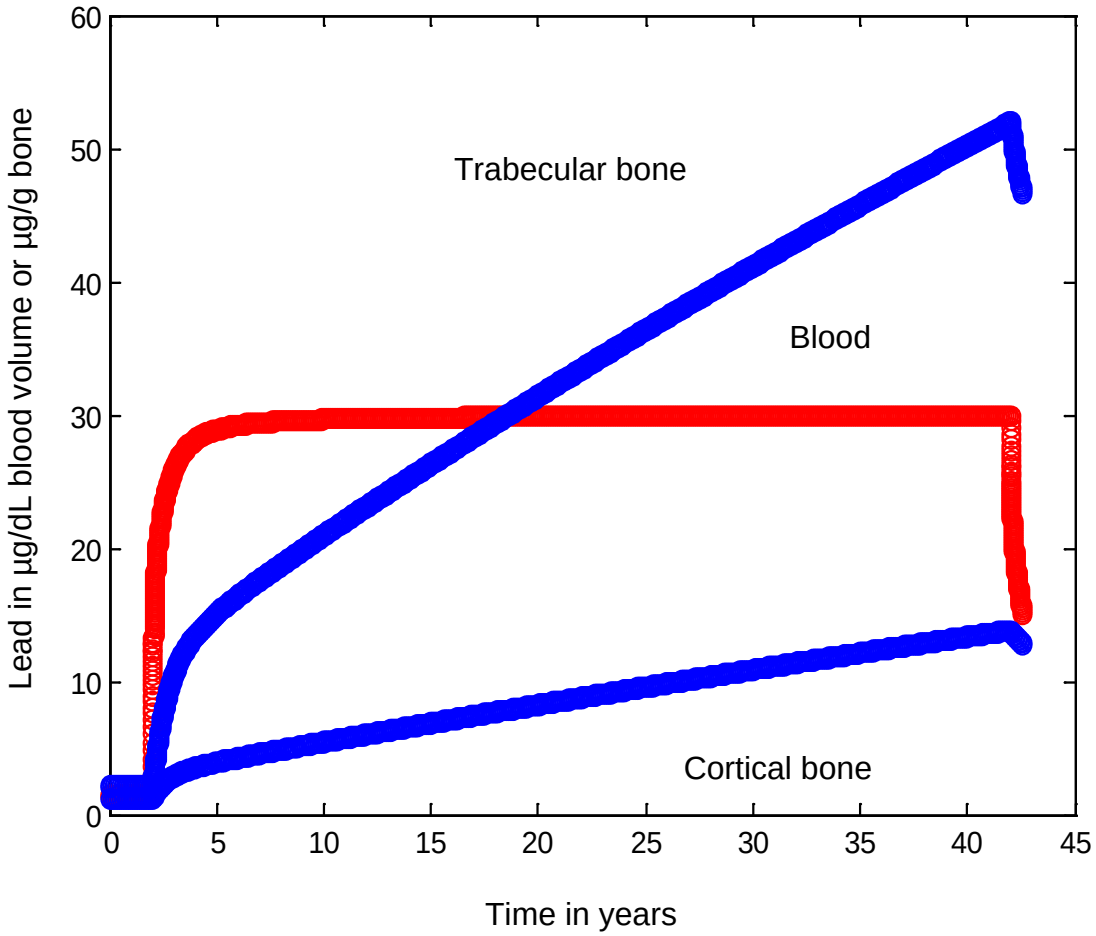
skeleton at a BLL of 60 µg/dL compared to 30 µg/dL because, as BLLs rise, an increasingly larger portion of lead remains unbound.

Figures 2 and 3 illustrate the effect on buildup and elimination of lead in a median worker's skeleton for two exposure histories (i.e., BLL of 30 reached after 40 years of exposure versus a BLL of 60 µg/dL reached after 40 years of exposure). In each scenario, after a year of exposure to non-workplace sources of lead alone, workplace air concentration is added to background for 40 years. Finally, workplace exposure ceases and background exposure levels become the only source of exposure for the remaining years as BLLs decline to the target BLL of 15 µg/dL. In Figure 2, the simulation is terminated when the BLL reaches 15 µg/dL after 210 days following the end of workplace exposure. In Figure 3, the simulation is terminated when the BLL reaches 15 µg/dL after 1045 days following the end of workplace exposure.

Note that the skeletal lead pool is not kinetically homogeneous. It is apparent in Figure 3 that turnover is faster in the mainly trabecular bone, which is about 20% of total bone, than in the mainly cortical bone, which is about 80% of total bone (Skerfving et al. 1987).

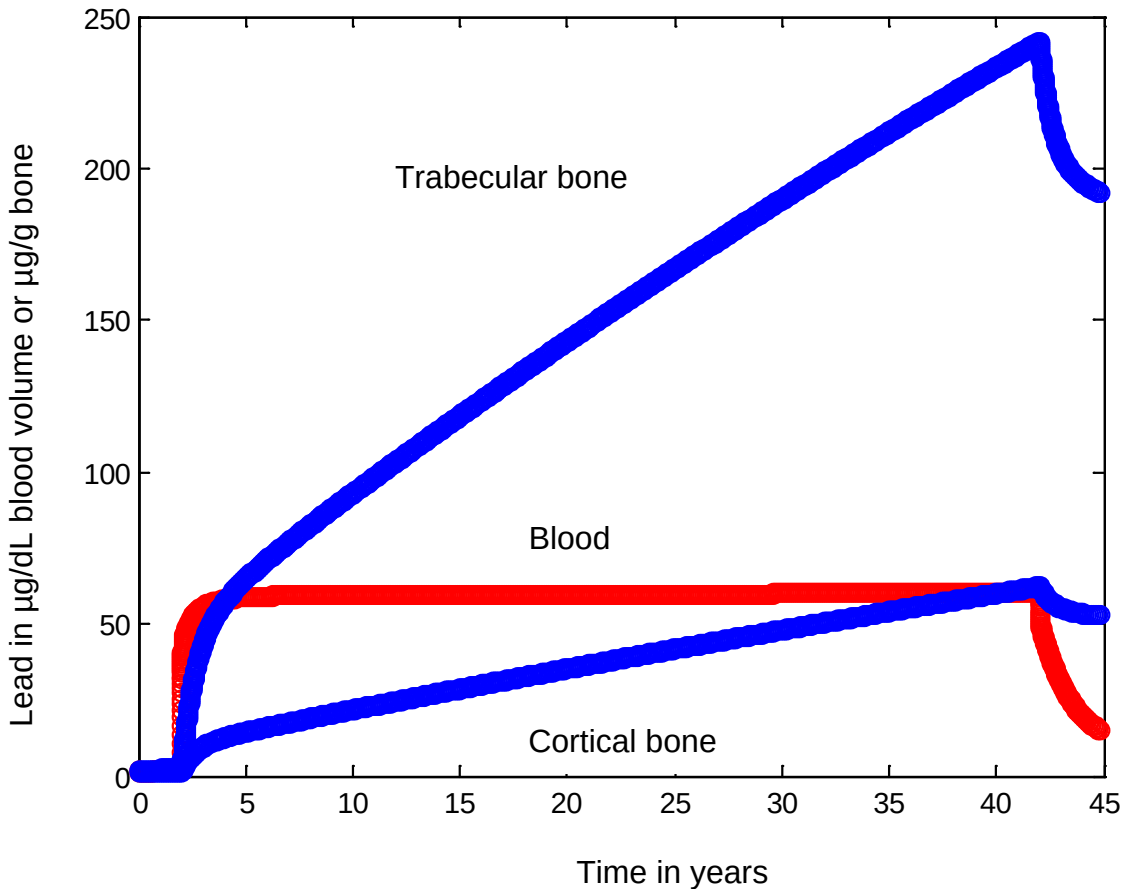
It can be seen in Figure 2 that BLL declines from a peak of 30 to 15 µg/dL before much lead is released from bone. For the occupational exposure scenario depicted in Figure 2, the predicted decline in BLL during the first few years after exposure corresponds mostly to declining lead in trabecular bone.

Figure 2: Modeled skeletal and BLLs for the median worker during and after workplace exposure (Leggett+ model)[1]



[1] Constant 8-hr TWA air concentration of 34 µg/m^3. BLL is 30 µg/dL at the end of 40 years; Bone mineral loss after age 35 is ignored. Adding bone loss rates of 10% per decade could result in a higher concentration of lead in bone than shown in this figure (Leggett et al. 1982; O'Flaherty 2000).

Figure 3: Modeled skeletal and BLLs for the median worker during and after workplace exposure (Leggett+ model)[1]



[1] Constant 8-hr TWA air concentration of 166 µg/m^3. BLL is 60 µg/dL at the end of 40 years; Bone mineral loss after age 35 is ignored. Adding bone loss rates of 10% per decade could result in a higher concentration of lead in bone than shown in this figure (Leggett et al. 1982), (O'Flaherty 2000).

2.3.2 Scenario two: Declining workplace air concentrations sustaining over 40 years a BLL reached in one year

CDPH-OLPPP also asked OEHHA to check whether there would be different times to decline if someone reached the limit BLL earlier than in the first scenario and stayed at that level for a number of years before being removed from exposure. Thus, in scenario two, we assumed workers were exposed to airborne lead for 1, 10, 25, or 40 years, resulting in BLLs of 20, 30, 40, 50, or 60 µg/dL within the first year of exposure. Then, the modeled airborne lead concentration was allowed to decline linearly in order to

sustain the BLLs at the level reached at the end of the first year (±10%) for the remaining years of exposure.

OEHHA conducted this exercise in two stages. First, OEHHA back-calculated the daily absorbed lead that would result in sustained 50th percentile (average worker) BLLs of 20, 30, 40, 50, or 60 µg/dL. Then, OEHHA back-calculated the PbA that would deliver those daily absorbed dosages for each of the 16 exposure scenarios using parameters listed in Table 1 for initial (pre-employment) blood lead concentration, background air lead concentration, transfer fraction of inhaled lead, daily uptake of lead (back-calculated from pre-exposure BLL) and breathing rates, and yearly exposure fraction.

Modeling sustained BLLs at a constant level over extended periods (greater than one year) required air concentrations to decline due to releases of accumulated skeletal lead. Modeled air concentrations decline linearly over the course of the exposure so that the BLLs peak after the first year and remain at a constant BLL for the duration of the exposure. Differences in air concentration at the end of the exposure period for a sustained BLL (scenario two) versus air concentrations for a BLL that reaches the limit BLL at the end of the exposure period (scenario one) are minimal (1% or less) (data not shown).

Scenario one and two result in the same, or almost the same, times to decline for all BLLs and all exposure periods (data for scenario two not shown). For example, even for a BLL of 60, for the 95th percentile worker, the time to decline to 15 µg/dL after removal from workplace exposure is less than a month longer (6.3 versus 6.2 years) for a worker with a sustained BLL of 60 µg/dL over 40 years compared to a worker who reaches 60 µg/dL only at the end of the 40-year period.

3 Discussion

OEHHA updated the approach taken by the Center for Policy Alternatives (CPA) to predict air lead/blood lead relationships through modeling workplace exposure to lead and its influence on overall body burden of lead in workers. This approach is explained in Section 3.1. The limitations to OEHHA's new model and remaining uncertainties in our approach are explained in Section 3.2.

3.1 Updates to approach taken by Center for Policy Alternatives to predict air lead/blood lead relationships

In developing the 1978 PEL, Federal OSHA considered the CPA's application of the pharmacokinetic Bernard model to predict air lead/blood lead relationships (Ashford et al. 1977).

The CPA application:

- modeled BLL following five years of exposure in a constant air environment.
- assumed a linear relationship between air lead and BLLs between 30 and 100 µg/100 g blood.
- assumed that at air lead concentrations below 12.5 µg/m^3 all particles are small and are absorbed with an efficiency of 37%; above 12.5 µg/m^3 all particles are large and absorbed with an efficiency of 8% (this is referred to as "Assumption C" by Federal OSHA [OSHA1978]).
- used a standard deviation (SD) of 9.5 µg/dL estimated from observed distributions of BLLs in individual industries in the 1970s independent of the distribution of air lead levels.

OEHHA also used a pharmacokinetic model to predict air lead/blood lead relationships but our approach differs from Federal OSHA's 1978 approach in several important ways. OEHHA:

- used the more recently developed Leggett+ model.
- modeled BLL at the end of a 40-year working lifetime at a constant air lead level. OSHA's 1978 approach is not sufficiently health protective because body burden does not reach equilibrium at 5 years but rather continues to rise with constant exposure (Barry 1975).
- accounted for nonlinear kinetics between BLLs and air lead levels. Research conducted since the Federal OSHA's 1978 standard shows that as BLLs rise above 25 µg/dL, the relationship between air concentration and BLL noticeably departs from linearity, likely due to red blood cell saturation (Azar 1975).

- developed an alternative approach for addressing particle size distribution based on lung dosimetry analysis and empirical data as suggested by Froines et al. (1995) (see Appendix B). Assumption C does not have an empirical basis and is not considered valid (Froines et al. 1995; Liu et al. 1996).
- applied a GSD of 1.6 with the assumption that BLLs are lognormally distributed (Griffin 1999), whereas Ashford applied a SD which implies that BLLs are normally distributed.

OEHHA compared model predictions given the approach described above to measurements from seven worker datasets and three postmortem data sets from the general population. These comparisons show that the model predictions are valid within the range of BLLs of interest to CDPH-OLPPP. However, every model has limitations and remaining uncertainties. A brief discussion of some limitations and uncertainty surrounding the Leggett+ model follows.

3.2 Limitations and uncertainty

3.2.1 Population BLL variability

In applying pharmacokinetic and other models to estimate changes in BLL in response to various lead exposure scenarios, we have employed distributions of BLL in the general population. The GSD we have chosen (1.6) was derived by Griffin et al. (1999) from several epidemiologic studies with paired environmental and BLL measurements in children (White et al. 1998). We cannot be certain that the BLLs in the worker population to which these estimates will be applied will be distributed in the same way as the BLLs in the children that were the basis for the GSD used in our modeling effort (Griffin 1999; U.S. EPA 2009). However, we checked this GSD against GSDs derived from data available on adults exposed to lead in controlled chamber studies and field studies of workers who wore personal breathing zone air monitors.

Using the method recommended by Griffin et al. (1999) for calculating GSD from site-specific data when conducting a risk assessment, we calculated GSDs from BLL data on adult workers and volunteers from Kehoe (Gross 1979, 1981), Griffin et al. (1975), Williams et al. (1969), and Azar et al. (1975). BLLs from these studies ranged from 10 to

93 µg/dL. We calculated GSDs by log transforming 8-hr TWA air and blood lead concentrations, grouping BLLs by levels of total lead intake, and deriving the GSD from the regression variance (mean squared error [MSE]). GSDs ranged from 1.4, 1.4, and 1.97 for the low (24 to 30 µg/d), medium (33 to 66 µg/d), and high (>100 µg/d) total intake groups respectively. We concluded that the GSD we have chosen is in the range expected for worker populations.

3.2.2 Breathing rate

We assumed a time-weighted average daily breathing rate of 26 m^3/day for workers. This rate is based on a weighted combination of sedentary, light, and moderate activity (see Appendix B). However, some sources might consider this breathing rate low for workers in strenuous activity jobs (U.S. EPA 1997). Workers breathing more or less than this amount may have greater or lesser lead exposures, respectively, depending on breathing patterns, lung morphology, and other factors.

3.2.3 Erythrocyte saturation

Almost all of the lead in blood binds to the erythrocytes (Booker et al. 1969). There is experimental evidence that the relationship between the plasma lead and blood lead concentrations is nonlinear (Barton 1989; Chamberlain 1985; Manton and Malloy 1983; Manton and Cook 1984; Marcus 1985a, 1985b, 1985c). This nonlinear behavior is not completely understood but may result from a reduced rate of flow from plasma into red blood cells (RBCs) as certain lead-binding components of these cells become saturated (Chamberlain 1985; Leggett 1993; Marcus 1985a, 1985b, 1985c; O'Flaherty 1991; Raghavan et al. 1980). Leggett provided an optional function that OEHHA incorporated into the Leggett+ model (Equation A-1, Appendix A). Leggett suggested a threshold of saturation at 60 µg/dL RBCs, corresponding to about 25 µg/dL of whole blood, and a maximum limit of saturation between 140 µg/dL and 350 µg/dL of RBCs. OEHHA eliminated the threshold for saturation, as it has no biological basis, and set the maximum limit of saturation to 270 µg/dL in RBCs (corresponding to a whole blood concentration of about 115 µg/dL). After making this and other modifications, we tested the model with several datasets from the literature. The results of these tests appear in

Appendix A of this report. However, the limit of saturation remains a source of uncertainty. There is also likely to be intra-individual as well as inter-individual variability in the saturation level (Fleming et al. 1998; Schwartz et al. 2000).

3.2.4 Lead's toxic effects could alter the kinetics of lead in the body

Exposure to toxic levels of lead can damage organ systems, thereby altering the uptake, distribution, and clearance of lead. Kidney damage has been reported among chronically exposed workers at BLLs as low as 30 µg/dL (Kim et al. 1996). More severe acute exposure produces anemia, which may lower the threshold of RBC binding, and kidney disease, which may decrease the rate of whole body elimination (Castellino et al. 1995; O'Flaherty et al. 1982). These factors could partly account for the wide variability in half-lives of BLL decline in studies of workers removed from high lead exposure. However, we are not aware of any studies that have examined the extent of such influences directly. None of the models specifically account for these toxic effects, except to the extent that these pathological processes may have affected the kinetics of lead in the individuals upon which the models were calibrated.

3.2.5 Particle size distribution

As stated earlier, the proportion of inhaled lead retained in the lung and in the extrathoracic regions of the respiratory tract and then gradually absorbed or cleared by the upward propelling action of the ciliated regions of the lungs and ingested is influenced by particle size distribution. Coarse particles tend to be cleared by ciliary action and swallowed where they can be absorbed by the gut. The percent absorption tends to be significantly greater in the lung than in the digestive tract. Therefore, one might expect that exposure to the same mass of coarser particles would lead to lower BLLs than exposure to finer particles. However, OEHHA's analysis of particle size distribution (explained in detail in Appendix B) led us to conclude that the overall transfer of mass to the blood is very similar.

One of the challenges in modeling air lead/blood lead relationships is what assumptions about particle size distribution to apply generically to the entire lead industry. There is some general knowledge on the types of industrial processes and construction tasks

that tend to generate coarse and fine particles (Froines et al. 1986; Hinds 1982; Hodgkins et al. 1991a; Hodgkins et al. 1991b; Liu et al. 1996; Park and Paik 2002; Virji et al. 2009; Vork 2003). However, information on the distribution of particle size for individual workplaces is not currently collected as part of a routine industrial hygiene program. Even if particle size distribution were available for different industrial operations and construction tasks, multiple operations often occur in the same workplace, and exposures can be mixed. In addition, occupational regulations must apply to the range of industrial and construction operations involving lead exposure, and incorporating varying particle size distributions into the model is impractical.

As stated earlier, the existing Federal OSHA standard addressed this issue by assuming that at air lead concentrations up to 12.5 $\mu g/m^3$ all particles are small and absorbed with 37% efficiency, and above this cut point all particles are large and absorbed with 8% efficiency. Federal OSHA applied a generic cutoff point because for some processes air concentration and particle size are correlated (OSHA 1978). However, this assumption has been challenged (Froines et al. 1995; Liu et al. 1996). OEHHA developed an alternative approach based on lung dosimetry analysis and empirical data.

In summary, we evaluated published particle size distribution data from a variety of industrial workplaces with differing operations that generate a range of particle sizes (fine to coarse). Using the reported MMADs and the MPPD2, OEHHA estimated the deposition and clearance in the head and lung of inhaled lead for a variety of occupational settings.

OEHHA's modeling of deposition and clearance is based on published particle size distribution data from a variety of real industrial workplaces. However, uncertainty remains because the actual particle size distribution for a given workplace on a given day may vary from the assumed particle size distribution. This may result in an over- or under-estimation of the amount of lead absorbed for a given air lead concentration, although our analysis indicates that particle size distribution (at least in the particle size range of 1 – 15 µm MMAD) plays a smaller role in the ultimate transfer of inhaled lead to blood than previously thought.

3.2.6 Gastrointestinal absorption

Early mass balance studies observed that the fraction of lead absorbed through the gut varies depending on the presence or absence of food (see section A.1 entitled “Lead biokinetics” in Appendix A). In addressing inhaled lead cleared from the lung by ciliary action and swallowed, OEHHA calculated a 24-hr TWA gut absorption assuming 10 hours fasting, 10 hours with liquids between meals, two hours intake with solids, and two hours in which no lead is swallowed. If the actual proportion of time in each of these conditions differs from OEHHA’s assumption, then either a lesser or greater fraction of lead would be absorbed from the gut.

3.2.7 Lead in bone

OEHHA was able to check the adjusted core model with bone measurements in one smelter worker after a long history of exposure documented through measurements of lead in blood over time. In addition, we compared the predicted ratio of lead deposited in trabecular/cortical bone to ratios from bone lead measured in nine retired smelter workers. Predicted ratios of bone lead were slightly larger than those observed in the nine retired workers (by a factor of about 1.8 or less depending on the length, timing and level of exposure history simulated).

To check predictions from the adjusted core model of lead in bone in active workers, it would have been ideal to have had access to measurements from studies that measured lead in trabecular and cortical bone over time from chronically exposed workers. We are aware of one such dataset (Fleming et al. 1997; Nie et al. 2005). However, we do not currently have access to these data. Should more data on exposure history, blood and bone lead measurements become available, further refinement of the model may be possible.

4 Summary and Conclusions

CDPH-OLPPP requested that OEHHA model the time it would take for workers’ BLLs to decline to a lower level - recommended by CDPH-OLPPP - following cessation of occupational exposure that resulted in BLLs ranging from 20 – 60 µg/dL with exposure histories of 1 to 40 years. OEHHA selected the Leggett model because it has an

optional algorithm that accounts for nonlinear kinetics as well as the flexibility we needed to conduct our own tests and, if needed, adjust model parameters to achieve optimal performance for our identified task. To achieve good performance from the model, OEHHA adjusted urine, bone, and blood parameters in the nonlinear Leggett model. These adjustments produced predictions comparable to data collected in the American Smelting and Refining Company (ASARCO) cohort and predictions of lead in separate tissue groups comparable to measurements from other lead workers and the general population. These studies are discussed and compared with OEHHA's modeling results in Appendix A. Studies that measured BLLs and PbA are discussed and compared with OEHHA's modeling results in Appendix B.

Despite the limitations and uncertainties discussed above, OEHHA believes that the modeled BLLs and corresponding air lead concentrations represent reasonable and scientifically defensible estimates. Our model predictions are in good agreement with experimental and epidemiological data. Most of the data used to test the Leggett+ model came from healthy male workers. Given the limitations and uncertainties mentioned above, blood lead predictions generated from this model may not reflect those observed in workers with personal characteristics or exposure conditions substantially different from the study subjects used to evaluate the Leggett+ model.

In the appendices of this report, we provide more detail about our process for selecting, evaluating, and applying the Leggett+ model. We adjusted the core Leggett model, added an exposure module, and tested Leggett+ for use in predicting chronic environmental and occupational exposures in adults. As described above, the Leggett+ model performed well in predicting observed BLLs. It should be noted that no effort was made to evaluate model predictions of exposure in childhood or in acute or short-term (less than 30 days) exposure scenarios. In addition, this new model has not been evaluated for chronic exposures leading to BLLs over 60 µg/dL.

A Appendix: Review, Selection, Modification, and Testing of Lead Models

In Appendix A, we describe our selection criteria for models to include in our review process. We then explain our evaluation criteria, baseline model requirements, and rationale for selecting the Leggett model. Finally, we describe the process we used to calibrate the Leggett model to fit observed data and test the final adjusted model.

CDPH-OLPPP outlined two tasks for OEHHA, which we have described in the main body of this report. The second task - to estimate the time required for workers with a long history of sustained high BLLs to eliminate lead down to levels recommended by CDPH-OLPPP - requires a time-dependent biokinetic model. Therefore, we focused first on models that can best represent this uptake and elimination process. We began our evaluation by reviewing the lead biokinetics literature. We reviewed the important attributes of lead uptake, distribution, and clearance that PBPK and biokinetic models need to take into account. This review helped to develop a basis for choosing a biokinetic model that would be suitable for the second task identified in the main body of this report. A summary of our findings from that review follows.

A.1 Lead biokinetics

Lead enters the body principally through the lungs and the digestive tract where differing amounts from each pathway are absorbed into the bloodstream. Upon entering the bloodstream, it is rapidly transported into the liver, kidney, bone, spleen, lung, heart, and skeletal muscle. Elimination is primarily through the kidneys and feces, secondarily through sweat, hair, and nails.

A.1.1 Pulmonary deposition and clearance

Hursh et al. (1969) estimated that at nominal breathing rates, adult lungs transfer 35% of inhaled lead mass suspended in ambient air to blood. However, the amount of lead deposited in the lungs and subsequently absorbed into the blood depends on several factors. The deposition rate and the region of deposition depend on the shape and the size distribution of particles, as well as individual breathing rate (volume of air inhaled

per unit time). For example, Kehoe balance experiments published in Gross (1981), which included delivery of submicron (median count diameters from 0.05 to 0.11 µm) and micron (0.75 to 1.20 µm) particles, estimated pulmonary deposition after subjects engaged in a mix of sedentary and more strenuous work. Mean pulmonary deposition of submicron particles ranged from 20 to 71% and of micron particles ranged from 43 to 64%.

Clearance rates depend on the region of deposition (i.e., within or outside of the ciliated region) and on particle solubility. The ciliated regions of the bronchial tree carry particles back to the pharynx where they are swallowed and potentially absorbed through the gastrointestinal tract. In the alveolar region, clearance occurs mostly by absorption directly into the blood from the pulmonary tissue (Booker et al. 1969; Castellino et al. 1995; Dinman 1991; Monosson, 2011). However, some mechanical clearance also occurs in this region of the respiratory tract (ICRP 1994). For example, clearance by the macrophage system occurs for highly insoluble particles.

A.1.2 Gastrointestinal absorption

A large range of gastrointestinal absorption fractions (1% to 80%) has been reported in the literature. This wide range occurs in part because absorption of lead from the gastrointestinal tract depends strongly on a variety of factors, including the level of minerals, fat, protein, and vitamin D present in the intestines; the body's iron or zinc status; the amount of lead and the physical and chemical form administered; and the length of fasting (Leggett 1993).

Gastrointestinal absorption of lead measured in studies on adult humans falls in the following categories:

- intake with solids, 3% to 20% (Chamberlain et al. 1978; Flanagan et al. 1982; Harrison et al. 1969; Heard and Chamberlain 1982; James et al. 1985; Rabinowitz et al. 1976; Rabinowitz et al. 1980)
- intake with liquid between meals, 8% to 30% (Blake 1976; Chamberlain et al. 1978)

- ingestion with liquids after several hours of fasting, 30% to 70% (Chamberlain et al. 1978; Flanagan et al. 1982; Heard and Chamberlain 1982; Hursh and Suomela 1968; James et al. 1985; Rabinowitz et al. 1976; Rabinowitz et al. 1980)

A.1.3 Erythrocyte uptake and saturation

The ratio of lead found in red blood cells to lead in the plasma varies according to the dose and the time elapsed from absorption. However, 94-99% of blood lead is bound to the erythrocytes (Booker et al. 1969). Previous studies indicate that the relationship between the plasma lead and blood lead concentrations is nonlinear (Barton 1989; Chamberlain 1985; Manton and Malloy 1983; Manton and Cook 1984; Marcus 1985a, 1985b, 1985c). This nonlinear behavior of lead is not completely understood but may result from a reduced rate of flow from plasma into RBCs as certain lead-binding components of these cells become saturated (Chamberlain 1985; Leggett 1993; Marcus 1985a, 1985b, 1985c; O'Flaherty 1991; Raghavan et al. 1980).

A.1.4 Uptake and elimination from blood and soft tissue

A pulse dose of lead is distributed from the blood to other tissues with a half-life of about 30 days. Once released from blood, the highest levels of lead in soft tissue are found in the kidney and liver. Less lead mass is found in the lungs, spleen, heart, skeletal muscles, and brain. Although there is uncertainty about uptake and release time constants for other tissues, most are much slower than for blood. Retention curves for the liver and kidney exhibit multiple half-lives ranging from a few days to one year; half-lives range from two years in the brain to 3.5 months to 5 years in other soft tissue (Leggett 1993). This information was mainly obtained from animal studies, contributing to the uncertainty.

A.1.5 Uptake and elimination from bone

Constant exposure to lead leads to slow accumulation in the body because of the high affinity for bone and incorporation into the bone matrix. The same high affinity is true of hair and nails, which are considered elimination pathways. Lead substitutes for calcium, becoming part of the hydroxyapatite crystal during bone remodeling. Lead can also be

incorporated by diffusion into bone matrix without becoming part of the hydroxyapatite crystal. Bone thus acts as a “sink” for lead. Bone lead therefore has a long half-life of elimination when exposure ceases. Autopsy studies revealed that among occupationally exposed and non-occupationally-exposed young men, 95% of the lead body burden was in bone, with the other 5% in soft tissues (Barry 1975; Castellino et al. 1995). Based on data from Christoffersson et al. (1986) and additional measurements of lead in vertebral bone biopsies, blood, and urine of present or former lead workers, Skerfving et al. (1987) concluded the following for trabecular and compact bone:

- The skeletal lead pool is not kinetically homogeneous; turnover is faster in the mainly trabecular vertebrae than in the mainly compact finger bone.
- The “average overall half-life is probably 5-10 years.”

For occupational exposure scenarios, the predicted decline in total bone lead corresponds to a half-life of 10-12 years during the first few years after exposure. By 25 years after the end of exposure, the rate of decline slows to a half-life of 25-30 years (Leggett 1993).

An ideal model would incorporate each of the important factors reviewed above.

A.2 **Model screening**

Prior to selecting models for review, OEHHA reviewed publications that examined and compared earlier models, particularly those supporting the Federal OSHA standards for lead and issues surrounding the BLL/PbA relationship (Castellino et al. 1995; Hattis 1981; Liu et al. 1995). Based on a review of the biokinetics of lead in the adult human studies that measured air and blood lead concentrations in adult subjects, OEHHA considered five of the most recent human PBPK and biokinetic models published in the peer-reviewed literature and available for use in an accessible format. Accessible formats include descriptions from the literature that can be turned into functional modeling code, usable scripts that can be read by modeling software, or executable graphical user interface (GUI) programs.

Of the five models considered, the U.S. EPA All-Ages Lead Model had not been released in final form at the time of our review and therefore was not evaluated further. Only summaries of various model runs and not the code for the model itself are available. The U.S. EPA Adult Lead Model is a steady-state model and therefore not able to accommodate the time-dependent requirements of tasks outlined in the Scope of Work. Liu et al. (1995) evaluated some of the hybrid models described in Hattis (1981) and those developed by Batschelet et al. (1979), Bernard (1977), Bert et al. (1989), Marcus (1985a, 1985b, 1985c), and Rabinowitz et al. (1976). These investigators concluded that the Hybrid P and Bert models performed similarly and better than the other models. We chose to evaluate the Bert model instead of the Hybrid P model and forego evaluating the models already evaluated by Liu et al. (1995).

The remaining three models accommodate time-dependent changes in the lead body burden and were reviewed for meeting the general requirements of the above tasks:

- The Bert et al. (1989) model is available as a MATLAB script.
- The Leggett model (Leggett 1993; Pounds and Leggett 1998) is available as a FORTRAN script.
- The O'Flaherty (1993, 1995) model is published in Advanced Continuous Simulation Language (ACSL) code (O'Flaherty 2000) and available as a GUI program.

Our review focused on:

- important attributes of lead uptake, distribution, and clearance for evaluating PBPK and biokinetic models.
- model structure, key parameters, and behavior of Leggett, O’Flaherty, and Bert models relative to chronic exposure to lead among workers.
- lead elimination from blood, soft tissue, and bone.
- flexibility to adjust internal parameter values to fit additional occupational exposure data if needed.

Multi-compartmental models, such as the Bert, Leggett, and O'Flaherty models, can be used to predict BLL over time. Compartment lead concentrations are determined from the lead masses and compartment volumes. The models simulate lead biokinetics as several interconnected tissue compartments that exchange lead between tissues and the central compartment using one of two approaches: The O'Flaherty model simulates exchanges between plasma and soft tissues as flow-limited processes and exchanges between plasma and bone as a combination of flow-limited and diffusion-limited processes. The Bert and Leggett models are diffusion-limited, i.e., they assume that exchanges between the various compartments are governed by rates of diffusion across compartment boundaries, represented as first-order rate constants.

In the next section, we describe each model in its original form and briefly summarize any subsequent modifications.

A.2.1 Bert model

Bert and co-workers developed a biokinetic model to predict BLLs in the general population (Bert et al. 1989). They built their model based in part on previous work of Batschelet et al. (1979), Bernard (1977), Marcus (1985a, 1985b, 1985c), and Rabinowitz et al. (1976). They calibrated their model using long-term changes in levels of lead in cortical bone in autopsy studies by Barry (1975). This adjustment allowed them to correct some of the shortcomings of prior models developed by Rabinowitz et al. (1976) and Bernard (1977).

A.2.1.1 Original Bert model

The Bert et al. (1989) model is comprised of six well-mixed compartments - two uptake compartments (lungs and digestive tract) and four transfer compartments (blood, tissue, trabecular bone, and cortical bone). The transfer of lead is represented as a set of four first-order differential mass balance equations with substantially different rates of transfer of lead for each of the four compartments. Bert et al. (1989) assumed that blood volume is proportionate to body weight and scaled blood volume to include soft tissue and bone volumes. There are four elimination pathways – exhaled air, feces, urine, and

other excreta (hair, nails, and sweat). Tissue volumes are linked to blood volume, which is a function of body weight.

Short-term changes in body burden in the model were calibrated to the data collected by Rabinowitz et al. (1976) on bone lead levels from cross-sectional autopsy data, and one subject from the experimental data collected by Griffin et al. (1975). The calibrated model was tested against experimental exposure data from three other study subjects in the Griffin et al. (1975) study. Simulations from the Bert model appear in the Meridian report cited in the preamble to the Federal Lead in Construction standard (Meridian Research Inc. 1992).

The Bert et al. (1989) model was designed to predict BLLs in the range found in the general population, BLLs significantly below those found in occupationally exposed cohorts.

A.2.1.2 Bert model modifications

Vork (2003) added an exposure module and a means for estimating the initial values of lead in each compartment as a function of pre-exposure BLL. Vork tested Bert's model on blood lead measurements taken during short-term exposures (i.e., 1 to 3 months) on a bridge rehabilitation project (Sussell et al. 1992). The investigator found that the model predicted measurements reasonably well (Vork 2003).

A.2.2 Leggett model

The Leggett (1993) model accounted for more of the known biokinetic factors than the model by Bert et al. (1989). The original linear form of the Leggett model describes the age- and time-dependent distribution and excretion of lead injected directly into blood. Leggett also included separate models for the nonlinear kinetics of lead in blood when red blood cells begin to saturate, for particle deposition and clearance, and for gastrointestinal deposition and clearance. The conceptual basis of this model relies on earlier studies of alkaline earth metabolism in adult man (Leggett 1993).

A.2.2.1 Original Leggett model

The Leggett model includes 13 well-mixed compartments. There are three soft tissue compartments (rapid turnover, intermediate turnover, and tenacious retention). There are two liver compartments, three kidney compartments, and a brain compartment. There are four bone compartments (cortical surface and volume, and trabecular surface and volume). Leggett also provides separate models for the respiratory tract and the gastrointestinal tract (Leggett 1993).

Although six sets of parameters are included as a means of characterizing the age-dependent behavior of lead in the growing body in the published Leggett (1993) model, we focused our review on the adult portion of the model because we were only interested in modeling adult worker exposure. Age dependence refers to inclusion of children with their pharmacokinetic differences from adults into the model. Our review was, therefore, limited to the parameter set that represents the adult body (i.e., ≥ 25 years of age).

The Leggett (1993) model was originally calibrated based on lead balance studies in healthy adults receiving lead tracers by injection, ingestion, or inhalation; postmortem measurements in environmentally exposed men, women, and children; and biopsy and autopsy measurements on occupationally exposed subjects. These data were supplemented with experimental, occupational, environmental, and medical data on the biokinetics of elements with physicochemical properties similar to those of lead and with findings from lead studies in laboratory animals.

Compartment volumes in the model are assumed to be a function of body weight. Tissue uptake and loss are defined in terms of transfer half-lives. A pulse dose of lead is assumed to enter the bloodstream and distribute rapidly to tissues and RBCs. Once a peak RBC content is attained, the RBC content and hence the total blood content begins to decline with a half-life on the order of 30 days. Exchanges between a diffusible plasma compartment and non-skeletal tissues are modeled as first-order.

The gastrointestinal tract is modeled as four anatomically-based segments, with absorption occurring only from the small intestine. Liver and kidney each consist of two

sub-compartments. Half-lives range from a few days in some parts of the liver and kidney to one year in other parts of these organs, two years in the brain, and 3.5 months to 5 years in other soft tissues (Leggett 1993).

Lead in blood distributes to a diffusible fraction, a plasma-bound fraction that is not diffusible, and the red cells. The relationship between plasma and red cells is nonlinear. This non-linearity becomes noticeable above a concentration of about 25 µg/dL of lead in whole blood or 60 µg/dL in RBCs. This change in kinetics may result from a reduced rate of flow from plasma into RBCs as certain lead-binding components of these cells become saturated. Leggett provided a separate function for the model to account for the effects of RBC saturation illustrated by Pounds and Leggett (1998) in Figure 6 of their publication. Equation A-1 represents this nonlinear function for the fraction of lead deposited in RBCs.

Eq. (A-1): RBC deposition fraction = baseline deposition fraction x [1.0 – (lead concentration in RBCs – threshold concentration) / (saturation concentration – threshold concentration)]$^{1.5}$

Leggett (1993) suggests 60 µg/dL for the RBC threshold (about 25 µg/dL whole blood) and a range from 140 µg/dL to 350 µg/dL for the limit of RBC saturation (62 µg/dL to 154 µg/dL whole blood).

There are five elimination pathways considered in the model – urine, feces, sweat, exhaled air, and other excreta (losses in hair, nails, and skin). Two major elimination pathways for absorbed lead are through urine and feces, with the other elimination pathways playing a minor role in overall excretion.

For the long-term retention of skeletal deposits of lead, the Leggett (1993) model is based on rates of bone remodeling. The rate of elimination from the adult skeleton was compared in part to data from occupational studies. During the first few years after the end of modeled exposures, the predicted decline in total bone lead levels corresponds to a half-life of 10-12 years. The duration of half-life increases to 25 years by 25-30 years post-exposure.

A.2.2.2 Leggett model modifications

Brito et al. (2005) derived bone transfer parameters from measurements in a cohort of over 300 active smelter workers in New Brunswick, Canada. As part of this investigation team, Nie et al. (2005) compared predictions of bone levels from the linear Leggett model (i.e., the Leggett (1993) model without the RBC saturation function) to bone levels of lead measured from the entire cohort of retired smelter workers. BLLs were monitored frequently following retirement of these workers during a period from 1966 to 1999 (Fleming et al. 1999). Average BLLs among these workers declined from about 70 µg/dL in the 1960s to 25 µg/dL in 1996 (Fleming et al. 1997).

In 1994 and 1999, measurements of lead were also taken from heel (trabecular) and tibia (cortical) bones on a subset of these workers. Nie et al. (2005) condensed the original Leggett model (without a RBC saturation function) into a three-compartment model (cortical bone, trabecular bone, and blood), used blood lead measurements to model exposure histories, and compared the trabecular and cortical bone compartment predictions to X-Ray Fluorescence (XRF) measurements of lead in bone mineral from the cohort of smelter workers. These investigators concluded that bone predictions using the linear version of the Leggett model consistently under-predicted levels of lead in cortical bone and substantially under-predicted lead in trabecular bone in these workers.

Nie et al. (2005) showed that lowering the transfer coefficients for both cortical and trabecular bone, thereby increasing the half-life in bone, improved the fit to measurements taken from the tibia (cortical) and calcaneus (trabecular) bone by XRF methods. After modifying bone transfer rates in the simplified Leggett model, Nie et al. (2005) checked the performance of the altered Leggett model by fitting the blood lead histories from each worker to blood lead predictions from the model and evaluated the bone lead predictions as a function of each worker’s blood lead history. Nie et al. (2005) concluded that elimination rates were age-dependent and published five age-specific models, which predicted bone levels much closer to those predicted by the original (linear) Leggett model. In addition, the authors observed that older workers had a history of higher exposures and that change in transfer rates from bone to blood with

age in Nie et al.'s alterations of the original Leggett model is also affected by exposure history (Nie et al. 2005).

Nie et al. (2005) highlighted their comparison of the predictions of BLL decline among retired workers using the linear model structure and parameters for adults published in Leggett (1993) without the RBC saturation component and the Nie et al. (2005) simplification of Leggett's model. Nie et al. (2005) did not do a comparison of the predictions of the Leggett (1993) model including the saturated RBC function to the retired worker data. This added nonlinear function would have produced a much higher level of lead in the skeleton during years when BLLs were much higher relative to the levels at the time each worker's retirement. Hence, the nonlinear model would have predicted levels of lead in bone much closer to those observed in the retired New Brunswick smelter workers.

A.2.3 O'Flaherty model

O'Flaherty (1991) published her model in 1991 and then continued to update it over a period of ten years, adding in differences with age in bone turnover, red blood cell saturation, and gender differences in model parameters during adulthood (O'Flaherty 1991, 1993, 1995; O'Flaherty et al. 1996; O'Flaherty et al. 1998; O'Flaherty 2000). Bone turnover in adults and differences in bone turnover between males and females were acknowledged but not addressed directly by Leggett in his model (Leggett 1993).

A.2.3.1 Original O'Flaherty model

The O'Flaherty PBPK model was originally structured as a rat bone and blood model with compartments for liver, kidney, other well perfused tissues, and poorly perfused tissues (O'Flaherty 1991). The human model was parameterized based on human data whenever possible, but in a few instances, data from experimental animals were used. The human model is both age- and gender-dependent, and addresses multiple pathways of exposure and the biokinetics of lead in children as well as adults (O'Flaherty 1991, 1993, 1995, 1996; O'Flaherty et al. 1998; O'Flaherty 2000).

The two uptake compartments are lungs and digestive tract. Elimination is via the liver (30%) and kidneys (70%). Cardiac output, clearances, and organ and tissue volumes

are expressed as functions of body weight and age. There are five different point estimates of body weight for different age ranges; two for the early childhood phase of growth and three for the subsequent adolescent growth spurt and stabilization at mature adult weight. Other anatomic and physiologic features of the model are tied to body weight.

In this model, the lead mass fluxes in soft tissues are limited by the rates of delivery of lead to the tissues, i.e., the product of the plasma lead concentration and the rate of plasma flow to the tissue. This model assumes lead partitions and equilibrates instantaneously between plasma and soft tissues. Tissue volumes, blood flow rates, and bone turnover rates are linked to body weight by expressions that reproduce physiologic measurements. The model treats glomerular filtration rate as a function of body weight and age, becoming nonlinear at one year of age.

Lead is incorporated into forming bone and returned to plasma as bone is resorbed. O'Flaherty used calcium isotope uptake studies to estimate rates of new bone accretion (bone remodeling) in the model. The loss of lead from blood is modeled as a triphasic exponential function with 42% eliminated with a half-life of 57 days, 16% eliminated with a half-life of 1.3 years, and the remainder lost with a half-life of 24.4 years. The latter slopes are consistent with the input to the blood from soft tissues and the skeleton, respectively.

A.2.3.2 O'Flaherty model modifications

O'Flaherty published updates of the human model largely based on new information from studies of lead in cynomolgus monkeys and trend curves for skeletal mass in men and women (O'Flaherty et al. 1996; O'Flaherty et al. 1998; O'Flaherty 2000). These publications characterized the relationship of plasma lead concentration to blood lead concentration and further adjusted bone parameters by increasing the diffusion and permeability constants by a factor of five and accounting for bone loss in adulthood. Further suggested alterations based on worker data also appeared around the same time (Fleming et al. 1999). Briefly, Fleming et al. selected a subset of workers from the same lead smelter population as Nie et al. (2005) described above for an initial

evaluation of the 1993 version of the model. Detailed blood lead records from two hiring groups comprised of 10 workers with long exposure histories and 10 workers with more recent exposure histories were used to derive oral and inhalation exposures as model input. In addition, bone and blood lead measurements of lead were taken after a 10-month strike and again three years later. These investigators simulated bone lead levels relative to each worker's cumulative blood lead index and concluded that model predictions did not distinguish between hiring groups and the model over-estimated amounts of lead in cortical bone relative to the worker data. In addition, a sensitivity analysis indicated that a reduction in red cell lead-binding coefficients and/or a reduction in the parameter representing rates of bone mineral formation would bring model predictions closer to measurements of bone in the smelter worker cohort.

Reducing the red cell coefficients in the O'Flaherty model had the effect of making the plasma lead/whole blood lead ratio more extreme at high (above 60 µg/dL) blood lead concentrations – leading to proportionately higher estimated uptake of lead to bone. In addition, lowering bone mineral formation rates in the model would reduce the transfer of lead to trabecular and cortical bone, respectively.

The investigators then evaluated the revised version of the O'Flaherty model for the smelter population as a whole. The revised model explained trends for the accumulation of lead in cortical bone and the release of lead from bone stores. However, the authors concluded that model predictions for the accumulation of lead in trabecular bone did not track observed levels in the calcaneus (mostly trabecular) (Fleming et al. 1999).

The modeled lead concentrations for trabecular bone were 2- to 5-fold less than those observed in the mostly trabecular calcaneus bone and similar to the under-predictions observed by Nie et al. (2005) of the Leggett (1993) model without the RBC saturation function. In addition, Fleming et al. mentioned that human lead concentrations measured for several trabecular sites have suggested higher uptake and/or lower turnover of lead than demonstrated by the model.

Independently, O'Flaherty (2000) altered a 1998 version of the human model by adding bone loss coefficients as a function of age and gender in older adults. O'Flaherty

adjusted her model to account for bone changes in adulthood because peak bone mass is known to be reached between ages 25 and 30 and then begins to slowly decline. To account for the release of lead from this slow loss of bone after age 30, a first-order loss of bone was incorporated into the existing model. O'Flaherty calibrated bone loss predictions to quantitative estimates of cortical and trabecular bone mass as functions of age from International Commission for Radiological Protection (ICRP) trend curves for skeletal mass in men and women to age 60. This calibration introduced cortical bone losses of 3% per decade and trabecular bone losses of 7-11% per decade after age 30 into O'Flaherty's latest revision (O'Flaherty 2000).

We obtained a GUI version of O'Flaherty's model, which allows the user to alter exposure levels, hematocrit, and body weight, and to view 21 fixed internal parameter settings. We were not able to check that the computer code describes the intended structure of the O'Flaherty model or adjust internal parameters. However, we were able to see that internal parameter settings are consistent with those published in O'Flaherty (2000).

This model handles some physiologic functions differently for males and females even after accounting for body weight. The model predicts a 49% decline in BLL in women and a 51% decline in men in the first year following removal from 50 $\mu g/m^3$ lead exposure and predicts lower BLLs for women than for men for the same exposure scenario. In addition, pregnancy and lactation, both of which would influence lead pharmacokinetics, are not modeled explicitly. A single linear function describes respiration rates as a function of body weight in both sexes up to one year of age. After one year, the linear slopes for males and females diverge. This is consistent with the measured results of Popovic et al. (2005).

A.3 Model selection

In deciding which of the models reviewed above was most appropriate for the tasks outlined in the report, OEHHA considered whether the model in question:

- incorporates nonlinear changes in how the body distributes and eliminates lead during environmental as well as occupational exposures.

- can be altered if needed to improve predictions for a broad range of exposure conditions inherent in lead-related work.

Bert et al. (1989) did not incorporate the influence of RBC saturation into his model, stating that at low levels of exposure, such as those found in the general population, nonlinearities involved with lead transfer or distribution are not expected to be a concern. However, for the purposes of modeling exposure scenarios for Tasks 1 and 2, significant nonlinearities would be expected, for example, in the distribution of lead due to RBC saturation (Leggett 1993). As BLLs rise above 25 µg/dL, the relationship between air concentration (exposure level) and BLL noticeably departs from linearity. Ignoring this nonlinearity dramatically underestimates levels of lead that accumulate in bone. Therefore, we determined that the Bert model was not suitable because it ignored changes that occur when BLLs exceed about 25 µg/dL and RBC saturation begins to be a concern (Bert et al. 1989). OEHHA did not attempt to create a hybrid of Bert's model and Leggett's algorithm for RBC saturation since the biokinetics in the Bert model were less detailed than in the Leggett model. Consequently, OEHHA did not consider the Bert model any further for the purposes outlined in this report.

O'Flaherty modeled the growing body, initially scaling her model developed for rats to humans, and then revising it with data from monkeys and humans. Thus, her model was not designed with adult workplace exposure in mind initially. Some of the animal kinetics data may differ from the kinetics of lead in human bones, for example, in workers subjected to long exposure periods in adulthood (O'Flaherty et al. 1998). As new data became available, modifications to the O'Flaherty model have been introduced in the literature to improve predictions in occupationally exposed workers.

The O'Flaherty model available to OEHHA is in the form of a GUI with only a limited ability to alter some parameter values. To use the O'Flaherty model for the purposes outlined in this report would have required that we translate the published ACSL model format to a newer form of ACSL or to a form executable in MATLAB. The ACSL published model is very lengthy and translating the model to a usable format was beyond the scope of this project. Because the GUI model did not meet our criterion for

flexibility to adjust internal parameter values to fit additional occupational exposure data, we did not consider it further.

Given the evidence presented by the work of Brito et al. (2001), Fleming et al. (1997, 1999), and Nie et al. (2005), it is apparent that both the original O'Flaherty model and the original linear form of the Leggett model under-predict lead levels in trabecular bone with the high exposures seen in workers. However, Leggett provided an optional algorithm that could be added to the linear model code easily which allows the user to correct for this under-prediction. In addition, the Leggett model gave us a great deal of flexibility to adjust internal parameter values to fit occupational data by publishing a much simpler mass-transfer structure than the volume and flow structure published by O'Flaherty. Therefore, we chose to work with the nonlinear Leggett model from this point forward for the purposes outlined in this report.

A.4 Further evaluation and adjustment of the nonlinear Leggett model

Leggett calibrated his model for lower-level environmental exposures that are quite different from the higher-level, chronic occupational exposures that CDPH-OLPPP asked OEHHA to model. Therefore, it was essential to check the performance of the model with data providing lead levels in bone or blood after chronic exposures relevant to lead workers. We were able to obtain additional data of this nature which allowed us to compare BLL and bone predictions from the Leggett model with observations from studies of workers with chronic exposure.

A.4.1 Coding integrity

Before we could evaluate the nonlinear Leggett model, OEHHA translated Leggett's description of his model from Leggett (1993) into code so that we could run it using MATLAB. This made it possible to add the nonlinear algorithm to Leggett's original model. This re-coding effort was validated by comparing predictions from MATLAB to predictions from the FORTRAN-coded form of Leggett's model with and without the algorithm depicting RBC saturation (personal communications with R. Leggett 2011).

Dr. Leggett provided the FORTRAN output for model runs with the following exposure inputs:

1. injection: acute input of 1 µg lead to blood
2. ingestion: acute input of 1 µg lead to stomach contents
3. ingestion: chronic input of 1 µg/day of lead to stomach contents for 20,000 days

Dr. Leggett provided time series model output with calculated organ or compartment lead contents as a function of time for three intake scenarios for a male worker, assuming there is no lead in any compartment before the acute intake or start of chronic intake. Gastrointestinal (GI) uptake is assumed to be 15% for both the initial lead input to stomach and lead endogenously secreted into the small intestine (SI). The following GI transfer coefficients were applied:

- 24/day from stomach to SI,
- 6/day from SI to upper lower intestine (ULI),
- 1.8/day from ULI to lower intestine (LLI), and
- 1/day from LLI to feces.

The transfer coefficient from urinary bladder to urine is 12/day.

Linear RBC kinetics is assumed in all three cases.

Leggett also provided model output for the nonlinear case where uptake of 100 µg/day of lead to blood occurs continuously for 10 years (3650 days). To simplify comparisons Leggett assumed that there is no lead in the body at the start of intake.

Dr. Leggett provided the output values for blood lead concentration (µg/dL) over time with the nonlinear case as well as the contents (µg) of

- extra vascular fluid (EVF),
- liver,
- kidneys,
- brain, and
- bone.

OEHHA assessed concordance between Leggett's output and that generated by MATLAB using analysis of variance at distant time points. The difference between values at distant time points was about four percent or less, which is considered a good fit (data not shown). This finding increased our confidence that we recoded the model correctly.

A.4.2 Assessing model performance

Having recoded the model, our next aims were to 1) determine how well the nonlinear Leggett model predicts the dynamics of worker exposure, removal from exposure, and the time required to eliminate lead in a worker's blood following exposures in the range of interest to CDPH-OLPPP, and 2) refine the model, if necessary, to improve its predictive ability for chronically exposed workers.

OEHHA's assessment of model performance proceeded in two phases. In phase one, we checked how well the nonlinear Leggett model predicted BLLs in a cohort of chronically exposed lead workers after a lengthy strike. In phase two we made changes to selected model parameters to improve the fit of the model to observed worker data and tested the performance of the adjusted model.

A.4.2.1 Phase one assessment: Preliminary assessment of model performance

Methods for phase one

In order to test overall model performance we compared the BLLs measured in a large cohort of workers at the end of a long strike with: 1) BLLs predicted by the nonlinear Leggett model using Leggett's suggested parameter values, and 2) BLLs predicted by the model after adjusting the RBC saturation value.

If the model were an accurate description of lead pharmacokinetics in chronically exposed workers, then there should be no systematic under- or over-prediction of BLLs and the average difference between BLLs observed in workers and those predicted by the model should be small. In addition, there should be no systematic relationship between model performance and job tenure, indicating that the bone and long-lived tissue compartments of the model are performing reasonably well.

The details of our assessment are presented below.

Data for phase one

Data from the open literature are available to assess the dynamics of BLLs after several years of workplace exposure followed by a decline of blood lead after exposure in workers' assigned work area ceases (Fleming et al. 1997; Nie et al. 2005, Hattis 1981; Lynam and Nelson 1981; O'Flaherty 1986; Schutz et al. 1987). Some studies of workers removed from workplace exposure (e.g., under a medical removal protection program), however, are confounded by ongoing workplace exposure because the workers continued to work somewhere else onsite where some lead exposure might still occur (O'Flaherty 1986). Therefore, OEHHA did not consider these studies suitable.

Nevertheless, we were able to locate five studies that described removal from lead-related work either due to a strike or retirement (Fleming et al. 1997; Hattis 1981; Lynam and Nelson 1981; Schutz et al. 1987; Nie et al 2005). Of these, two studies provided time-dependent assessments (modeled results) of BLLs at the individual level (Hattis 1981; Schutz et al. 1987), although Schutz et al. (1987) did not report measurements for individual study subjects. The most robust dataset was presented in Hattis (1981). Therefore we selected Hattis (1981) for assessing model performance.

Both Hattis (1981) and Lynam and Nelson (1981) conducted studies using data collected by the ASARCO smelter. These data included BLLs before and immediately after a nine-month strike at the ASARCO primary lead smelter in Glover, Missouri. The data include pre-employment BLLs for most workers and an estimate of pre-strike BLLs from complete histories of BLLs leading up to the strike in 1976. It also includes BLLs taken before workers were re-exposed. In their study, workers were included if they had at least two sets of pre-strike blood lead measurements taken within six months prior to the strike, while working, and a measurement taken within two days upon returning to work after the strike. The mean length of employment was six years.

Lynam and Nelson (1981) estimated that the mean post-strike BLL of 35 µg/dL was 63% of the mean pre-strike BLL of 56 µg/dL, from which a half-life of 403 days can be calculated. This group half-life estimate was used by the authors to extrapolate

individual BLLs at the end of the strike, using the individual data on BLL prior to the strike, in the absence of half-life data on each individual.

Hattis (1981) was able to provide more data from this cohort of workers in a report written for Federal OSHA. The additional data set included individual data on pre-exposure, pre-strike and post-strike BLLs, and years on the job for workers removed from exposure due to a nine-month strike. This data set provides BLLs after a sufficiently long post-strike interval to test how accurately each simulation predicts elimination from the skeleton as well as soft tissue. Since there is no reason to suspect that striking workers might have systematically different blood lead dynamics than workers as a whole, this data set is assumed to be representative of smelter workers generally. The information available for 66 workers included in the analysis appears in Table 3.1 of the Hattis (1981) report.

Phase one simulation

OEHHA followed Hattis' methodology to model the expected post-strike BLLs for these workers. The pre-employment BLLs range from 10 to 85 µg/dL. Hattis excluded three workers with pre-employment BLL of 60 µg/dL or higher. This is so high that he believed the individuals came from a population of workers with previous occupational exposure (Hattis 1981).

We excluded from the study another three subjects with post-strike BLLs lower than pre-employment BLLs, indicating previous occupational exposure to lead, and four subjects with post-strike BLLs higher than pre-strike BLLs, suggesting some ongoing occupational exposure during the strike. In these workers, previous and ongoing occupational exposure could have resulted in higher bone lead. Consequently, continued releases of lead from the bone could have confounded the relationship between the exposures experienced in the current job and their corresponding BLL. No information was available on the previous length of employment.

The attributes of the additional seven subjects we excluded did not significantly alter the average and standard errors for the attributes of the 66 subjects presented in Hattis (1981).

We set up our test of the model by back-calculating background and pre-strike total (background plus occupational) intakes for each worker from their unique pre-employment and pre-strike BLLs as estimated in Hattis (1981). Using those intakes, we simulated pre-employment and employment BLLs up to the time of the strike for each worker. We then applied the background intake only during the simulation of BLLs during the nine-month strike. Finally, we recorded the predicted BLL for each worker and compared it to each worker's measured blood lead at the end of the nine-month strike.

Results of phase one assessment

For each of the 59 subjects we derived a predicted BLL and compared it to their measured post-strike BLL. When we ran the simulation with Leggett's suggested parameter values (Leggett 1993), the average difference between the measured and predicted post-strike BLL was unacceptably large and indicated significant under-prediction of BLLs (data not presented).

In an attempt to improve the fit, we lowered the RBC saturation value from 350 µg/dL to 222 µg/dL (geometric mean of the upper and lower values given in Leggett [1993]) and reran the simulation. The average difference between measured and predicted post-strike BLL was 4.1 µg/dL, with a standard error of 0.97 µg/dL (individual data not presented). This indicated that the model was predicting BLLs 10 months after the end of workplace exposure that were 4 µg/dL lower on average than BLLs observed in the ASARCO cohort.

The adjustment to the RBC saturation parameter improved the fit but was still inadequate. This systematic under-prediction of BLLs, even with a lower RBC saturation parameter, suggested to us that the modeled bone lead levels were too low for chronically exposed workers (The full significance of this under-prediction of bone-lead levels will be shown later in phase two). Recommendations based on this model could result in: a) an air lead limit (or PEL) insufficiently low to maintain BLLs below a level CDPH-OLPPP determines adequately protective of worker health and, b) an underestimate of the removal time necessary for a worker's BLL to fall to a lower,

acceptable level. OEHHA felt that a model that more closely tracked the BLLs observed in available data was required.

A.4.2.2 Phase two assessments: Model calibration to observed data

In an effort to improve the predictive ability of various pharmacokinetic models, researchers have modified model parameters and then tested the fit of the adjusted model against observations. Hattis (1981) and Nie et al. (2005) adjusted bone parameters in the Hybrid and Leggett models, respectively, to fit the exposure experience of two different cohorts of smelter workers. However, neither of these models included the effect of RBC saturation at higher exposure levels that has been noted in the literature. In a formal sensitivity analysis of the O'Flaherty model, Fleming et al. (1999) found that adjusting bone and RBC binding parameters was vital to achieving a better fit between model output and observations. However, they did not achieve a good fit to bone measurements, nor did they compare blood lead predictions to observations of blood lead after modeling each worker's unique exposure period. O'Flaherty (2000) found that adjusting the plasma lead clearance parameter reduced blood lead over-predictions observed in her model at low-level exposures, but she did not attempt to test her adjusted model on data from occupational exposures. Our approach to selecting and testing adjustments to parameters in the nonlinear Leggett model (referred to as adjusted core model) is based on the knowledge gained from these efforts. Our methods and results are presented in detail below.

Objectives of phase two

The objectives of our model calibration effort were to:

- eliminate the difference between the average observed and average predicted BLL by adjusting selected parameters until the model predictions are in alignment with the observations in the ASARCO cohort data.
- produce a model that performs well regardless of job tenure, indicating that bone and long-lived tissue compartments are performing well.
- ensure that adjusted model parameters remain in line with data of very long-lived bone lead and lead in other tissues from chronically exposed workers.

- ensure that modeled distributions of Pb in bones and other tissues are in line with autopsy data from the general population.

Selection of parameters to be adjusted in phase two

The parameters we adjusted and tested are bone, blood, and plasma (via urine). We selected these parameters based on the work of Hattis, Nie et al., Fleming et al., and O'Flaherty described above.

Phase two model calibration

In an iterative process, OEHHA made changes to the selected parameters in line with chronic occupational exposures. We repeatedly compared the predicted results to the observed ASARCO cohort data and adjusted the parameters until the under-prediction was eliminated. As we made changes, we checked that the adjusted parameters remained in line with observations of blood, plasma, urine, and bone lead data obtained from both occupationally and non-occupationally exposed adults. The details of the adjustments and our tests of model performance are presented below.

Phase two tests of model performance

OEHHA performed a number of tests with the adjusted core model to determine overall model performance as well as check the impact of the adjusted model parameters on the distribution of lead to all tissue groups in the adult human body. These tests and their results are described below.

Test 1: Goodness of fit

In order to test overall model performance we again used the ASARCO cohort described earlier in the report, with one change - we excluded an additional 12 workers with BLLs above 60 µg/dL because these values are out of the range of interest of CDPH-OLPPP. For each of the remaining 47 subjects we derived a predicted post-strike BLL using the adjusted core model and compared it to the measured post-strike BLL.

Test 2: Model performance relative to job tenure

In his initial assessment of the Bernard model, Hattis observed that there is some tendency for longer job tenures to be associated with over-predictions of BLLs relative to the ASARCO strike data. Hattis pointed out that any linear tendency resulting in a p-value greater than 0.05 to 0.10 tentatively suggests a systematic difference between observation and expectation—the model might be giving a somewhat larger weight to job tenure than is warranted (i.e., less lead might be stored in slow-exchanging pools than called for in the model, or the rates at which the slow-exchanging pools accumulate and release lead might be somewhat off).

Based on Hattis' observation with the Bernard model of a potential association between model performance and job tenure, OEHHA decided to check the performance of the Leggett model in relation to job tenure using the same regression analysis technique. Specifically, we conducted a regression analysis looking at model performance (measured minus predicted BLL) relative to job tenure for the 47 subjects to test for a statistically significant trend. This analysis was performed using Microsoft Excel (2010).

Test 3: Model performance relative to measured bone lead levels in a smelter worker

Leggett (1993) based transfer rates from non-exchangeable bone pool to blood on histomorphometric measurements on human subjects and studies of retention of certain bone-seeking radionuclides in human subjects. Most histomorphometric measurements available at the time were on ribs and iliac crest, but there were also a few measurements for various long bones. Leggett assumed that turnover rates differ between trabecular and cortical bone by about a factor of six in the mature adult. He did not address differences in bone turnover during adulthood. Historic estimates of a single long-term turnover rate in the adult human skeleton have ranged from about 0.007/year to about 0.15/year. Leggett set the adult trabecular nonexchange bone to plasma transfer rate at about the midpoint of this range and the cortical nonexchange bone to plasma transfer rate about six times slower.

Leggett concluded from a survey of literature that only broad comparisons between model predictions and findings from measurements of bone lead could be made due to the paucity of information on the lead exposures reported by investigators stating that "…the rate of decline depends somewhat on the pattern and duration of the exposure, which affect the distribution of bone lead at the end of exposure" (Leggett 1993).

This limitation has been somewhat overcome by a more recent study that combined measurements of lead in the heel and tibia bones with a robust history of BLLs from the study of smelter workers reported by Nie et al. (2005) and Fleming et al. (1999). Nie et al. observed that more lead accumulates in trabecular bone than previously predicted by the Leggett model and the rate of accumulation differs by age, which is correlated with exposure history. This supports Leggett's statement that bone levels of lead depend on the pattern and duration of exposures. Therefore, we considered the Nie et al. data an important check for our adjusted model.

As described earlier, Nie et al. (2005) reported bone parameter adjustments for five age groups based on predictions from a simplified linear version of the Leggett model fit to bone and blood measurements from each age group. These workers were part of a cohort of adult workers from a smelting facility in New Brunswick, Canada (Fleming et al. 1997; Nie et al. 2005). Cohort BLL data were recorded routinely from the late 1960s. In the early 1990s, workers were enrolled in a bone lead study that collected lead levels from the heel (trabecular) and tibia (cortical) bones. Nie et al. (2005) reported measured and modeled cortical and trabecular bone lead levels for each of nine retired workers in a table. Blood and bone measurements plotted over time were available from a graph for subject #1.

Nie et al. derived new bone lead transfer rates by fitting the predicted to measured bone lead for each worker. This was accomplished by first deriving the lead intake according to the blood lead history and estimates of background levels in the population before and after 1970 (Nie et al. 2005). The authors found that bone parameter values substantially lower than those suggested by Leggett fit measurements of cortical and trabecular bone taken from chronically exposed smelter workers.

We were unable to get access to the full Nie et al. dataset, therefore our check is limited to one worker for whom both BLL and bone measurements were available or could be extracted from Nie et al (2005).

For this worker (subject #1), we extracted bone measurements from Table 1 and average BLLs for three major time periods (early high, after an initial reduction in exposure, and after removal from exposure) from Figure 3 in Nie et al (2005). We then used a method similar to Nie et al.'s for estimating intake during each time period based on the extracted BLLs. Finally, using the adjusted Leggett model, we modeled BLL, trabecular lead, and cortical lead levels four years after retirement and compared them to measured levels.

Although limited, this test allows us to check whether the adjusted core model provides reasonably accurate predictions of bone lead in chronically exposed workers. Prior researchers have also used data from a single worker or adult to calibrate and test models when additional data are not available.

> Test 4: Predicted and measured plasma and urine lead concentrations relative to whole blood lead concentrations in three worker cohorts

In Leggett's original model he assumed that the observed nonlinear relations between lead in blood and plasma, urine, or other fluids and tissues observed by several investigators (Marcus 1985a; Chamberlain 1985; O'Flaherty 1991; Raghaven 1980) result from a decrease in the transfer rate from diffusible plasma to RBCs as the concentration of lead in RBCs increases. Leggett set a baseline saturation (S) concentration at 350 µg/dL RBC based on data showing where the ratios urinary lead:BLL and plasma lead:BLL begin to increase rapidly in persons exposed for a long period to levels of lead found in the workplace in the 1960s and 1970s (Figures 13 and 14 in Leggett [1993]). In contrast, Leggett suggested that a much lower value for S, perhaps on the order of 140 µg/dL RBC, may better represent more rapidly increasing urinary lead:BLL ratios for a high, acute intake by a person with a history of low intakes (Figure 13 in Leggett [1993]).

In Leggett's equation for RBC saturation, he included a term that effectively ignores the onset of decreasing capacity for lead to bind in RBCs at lower levels of lead in whole blood. OEHHA chose to eliminate this term and therefore needed to recheck that the ratios of plasma and urine to whole blood lead after we made adjustments to the model were similar to those found by Leggett for chronically exposed workers. We also identified additional data sets of lead in plasma, urine, and whole blood in chronically exposed workers for further comparisons. These data sets and our analysis are described below.

Selection of data sets for Test 4:

OEHHA identified several studies in the literature which examined the relationship between whole blood, plasma, and/or urine lead levels measured in workers exposed to lead (Manton and Cook 1984; Lee 1982; Hirata et al. 1995; deSilva 1981; Cooper et al. 1973; Wang et al. 1985). From these studies OEHHA selected three datasets that provided individual data and documentation or indications of chronic exposure for checking model performance (Manton and Cook 1984; Lee 1982; Hirata et al., 1995).

Manton and Cook (1984)

Briefly, Manton and Cook examined serum, whole blood, and renal clearance levels of lead from 36 patients followed by either a medical center or a health science center in Dallas, Texas. For most of these patients, the source of lead exposure and/or the type of occupation were not reported. Twenty-five patients had other neurological disease or symptoms not involving heavy metal intoxication or motor neuron disease. The other 11 subjects were patients diagnosed with motor neuron disease.

Samples were collected at the convenience of the attending physician. Authors estimated that the lead concentrations from their methods for collecting and analyzing serum lead have no more than 20% uncertainty associated with them, and for blood and urine the uncertainty is less than 2%.

Whole blood, plasma, and urine lead measurements were taken from 36 patients; whole blood lead results ranged from less than 20 µg/dL to 150 µg/dL. Authors noted that at a blood lead concentration of 10 µg/dL, serum (plasma without clotting factors) lead is

0.25 µg/dL and then rises as a steep function of blood lead concentration. In Table 1 of Manton and Cook, serum lead levels ranged from 0.020 to 3.33 µg/dL. The authors did not report urine clearance data in relation to whole blood data.

The serum versus whole blood values that appear in Figure 2 were abstracted using GetData™ (version 2.24) given that tabular data for individual subjects were not published in Manton and Cook (1984). Although the full range of data was visible in the published graph, 23 data points were within a “hatched” area of the graph below 20 µg/dL whole blood. Therefore, we extracted individual data points in the range of whole BLLs between 20 and 70 µg/dL. Within this range, about 15 data points were extractable.

Lee (1982)

Lee examined 234 male lead workers employed in a storage battery factory in Korea who were tested for lead in blood and urine. In this study, the mean age was 28.4 years ± 6.5 SD and mean work duration was 4.4 years ± 3.8 SD. The mean area air concentration ranged from 70 µg/m^3 to 380 µg/m^3 among five workplaces.

All urine analyses were made on spot samples and all urine samples were corrected to a specific gravity of 1.016. A single sample was obtained from each subject. However, the timing of blood and urine tests was not included in the description of methods.

Average blood lead was 53.8 ± 19 µg/dL. Average urine lead was 119 µg/L ± 84. The values that appear in Figure 1 were abstracted using GetData™ and represent summary data (i.e., the mean for a given BLL ± 1 SD). Tabular data for individual subjects were not published in Lee (1982).

Hirata et al. (1995)

Hirata et al. followed for 15 months four workers exposed to an average ambient air concentration of 286 µg/m^3 in a Japanese factory that manufactures lead glass-based paints. These workers had at least two years of exposure in the factory prior to the start of the study. Data from one worker assigned for a short time (one month) to the sifting

work setting with a much higher average air concentration of lead (1.05 mg/m^3) were not included in our analysis.

Levels of lead concentration in ambient air in the workplace as measured by personal sampling ranged from 0.022 to 1.331 mg/m^3 (mean: 0.286; SD: 0.333) in 1989 in workplaces other than the sifting workplace.

Sixty sets of blood and urine samples were obtained from the four workers not assigned to the sifting workplace during a 15-month period.

Whole blood, plasma, and urine lead measurements taken from four workers (60 samples over 15 months) were 52.3 µg/dL ± 7.79, 0.52 µg/dL ± 0.20, 130 µg/L ± 62.4 (mean ± SD), respectively. Similarly, we used GetData™ to extract urine lead vs. whole blood lead and plasma vs. whole blood lead data from Figures 1 and 2 in Hirata et al. (1995).

Using the extracted data, we modeled the plasma lead and urine lead relationships to whole blood lead and then plotted the predicted versus observed relationships for the three worker cohorts.

Test 5: Comparison of modeled tissue lead distributions to measured lead distributions from autopsy data

As a final test, we compared postmortem data on the distribution of lead in various tissues in humans chronically exposed to a low level of lead throughout life with the distribution predicted by the original and adjusted Leggett models. This comparison allowed us to examine whether changes in bone, RBC saturation, and urinary clearance parameters had affected lead distribution in other tissues.

Leggett derived reference organ distributions from postmortem data collected in the 1960s and 1970s (Gross et al. 1975; Barry 1975; Tipton and Cook 1963, 1964; Schroeder and Tipton 1968). Leggett conducted an uncertainty analysis to derive upper and lower bounds on the distributions given the uncertainties inherent in the data (details described in Leggett [1993]).

Results of phase two assessment

Final adjusted parameters

Table A-1 presents Leggett's original and our final adjusted parameters for bone transfer and RBC saturation. For comparison we have also presented the parameters used by Nie et al. (2005).

Table A-1: Parameter values from Nie, Leggett and adjusted core model[1]

Parameter	Nie	Original Leggett – nonlinear	Adjusted core model
C-bone non-exchange to blood	1 to 27 x 10^{-5}	8.22 x 10^{-5}	1.6 x 10^{-5}
T-bone non-exchange to blood	0.4 to 22 x 10^{-5}	49.3 x 10^{-5}	1.97 x 10^{-5}
Blood to C-bone non-exchange	1.5 to 7.2 x 10^{-4}	46.2 x 10^{-4}	3.81 x 10^{-4}
Blood to T-bone non-exchange	2.8 to 6.3 x 10^{-4}	46.2 x 10^{-4}	2.82 x 10^{-4}
RBC Saturation	NA	350	270
RBC Threshold	NA	60	0

[1]Nie et al. (2005), Leggett (1993), and adjusted core model (this work); C-bone, cortical bone; T-bone, trabecular bone; RBC saturation, level in micrograms per deciliter red blood cell when cells reach binding capacity limit; RBC threshold, level in micrograms per deciliter red blood cell when cells noticeably start to show reduced binding capacity (Leggett 1993); NA, not applicable.

The final bone absorption values we used fall within the range presented by Nie et al. (2005). We eliminated the RBC saturation threshold value of 60 µg/dL as it has no biological basis. (Per personal communication with Dr. Leggett, the saturation threshold value was originally included for mathematical convenience.) We selected a RBC saturation value of 270 µg/dL RBCs (corresponding to 119 µg/dL whole blood) based on the value derived by O'Flaherty (1996). Finally, we adjusted urine parameters to help correct the BLL under-prediction and bring ratios of plasma and urine lead to whole blood lead into line with those observed in worker cohorts.

Tests of Model Performance

As described previously, OEHHA repeatedly tested model performance during the calibration process. Only the results of the tests performed with the final adjusted model are presented here.

Test 1: Goodness of fit test

Table A-2 lists the attributes among 47 smelter workers along with the estimate of fit between the model-predicted and observed BLLs.

Table A-2: Estimate of fit of predicted to observed BLLs for 47 smelter workers[1]

Subject	Pre-strike job tenure (days)	Measured pre-employment BLL(µg/dL)	Estimated pre-strike BLL(µg/dL)	Measured post-strike BLL(µg/dL)	Predicted post-strike BLL(µg/dL)	Measured minus predicted BLL (µg/dL)
5	3084	11	30.5	17	26	7
6	2266	14	38.2	36	44	-5
8	3080	10	57	41	34	0
14	3077	20	37.3	28	21	2
15	3080	10	35.3	10	42	5
23	3087	10	37.2	10	27	4
27	3084	20	34.1	32	44	-4
33	3071	21	39.9	24	31	-9
34	3071	17	26.7	20	25	-1
36	3070	35	49.9	44	35	2
39	3071	13	39.3	20	23	3
45	3066	22	52.3	37	25	6
47	3066	24	35.8	29	25	6
54	3060	34	43.9	38	29	5
59	3052	13	46.7	23	28	-1
62	3045	17	56.1	35	23	13
63	1960	20	42.4	34	34	6
67	3043	18	42.5	26	24	4
68	3045	24	57.4	40	38	-2
73	1960	20	32.2	31	37	10
88	1959	14	37.8	26	20	13
91	742	16	42.9	33	30	9

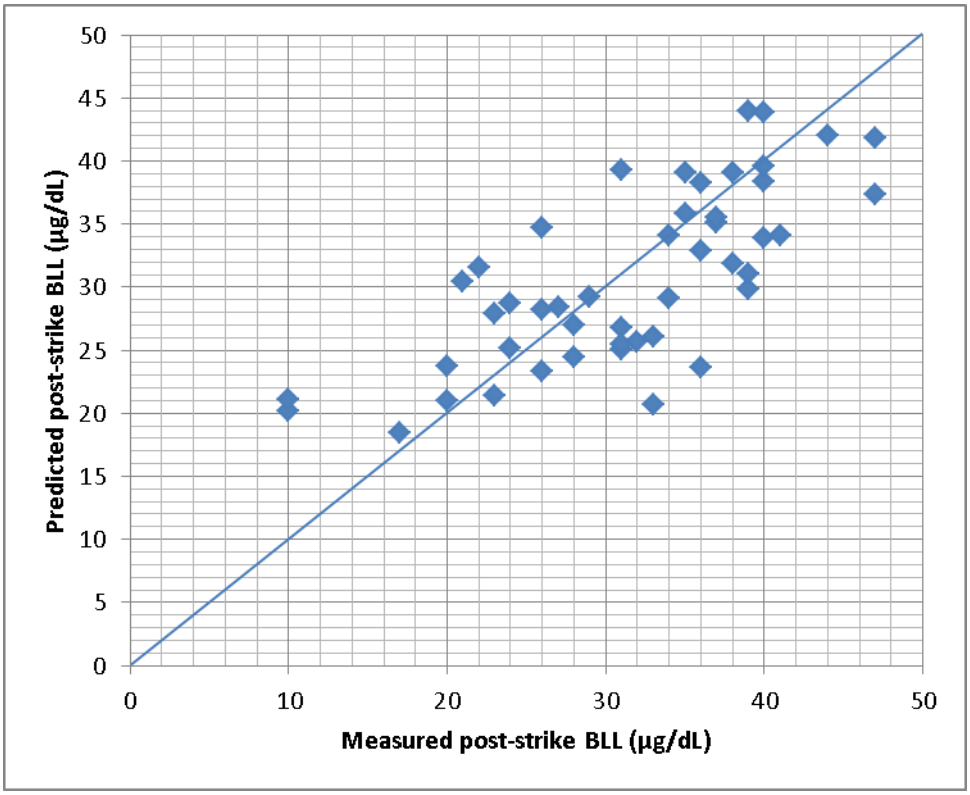
Subject	Pre-strike job tenure (days)	Measured pre-employment BLL(µg/dL)	Estimated pre-strike BLL(µg/dL)	Measured post-strike BLL(µg/dL)	Predicted post-strike BLL(µg/dL)	Measured minus predicted BLL (µg/dL)
101	1953	22	52.1	37	34	-8
106	1818	17	37.8	24	31	8
108	2979	33	43.9	40	32	6
115	2912	33	45.8	35	33	3
138	2928	10	52.4	21	39	-8
157	2667	27	54.5	31	39	-4
158	2660	26	42.4	36	30	-9
159	2653	18	49.5	38	38	2
161	1617	21	46.7	22	28	-2
177	1582	35	55.4	40	36	-1
188	2541	24	41	39	39	1
191	1499	19	39	31	28	-5
202	1288	26	60.4	47	39	-1
203	2485	16	55.2	26	29	0
218	1162	14	34.1	23	35	2
221	2415	20	43.7	39	42	2
225	2408	26	52.2	47	21	-1
226	2415	10	36.5	33	24	-4
227	1148	18	54.3	34	29	-5
237	1106	36	54.8	39	27	1
257	2346	34	41.6	36	20	-10
286	2268	12	41.8	28	34	7
288	2266	27	43.3	40	18	-1
299	2247	13	47.8	27	26	6
474	1960	17	38.5	31	21	-11
Average	**2433**	**20.4**	**44.3**	**31.5**	**30.6**	**0.9**
Standard error	**98.3**	**1.1**	**1.2**	**1.3**	**1.0**	**0.9**

[1] The attributes of the 19 subjects we excluded from the dataset did not significantly alter the average (Standard error) estimates of the 66 subjects presented in (Hattis 1981) for variables other than pre-strike BLLs. (job tenure 2433 (98.3) versus 2255 (102) days, pre-employment BLL 20 (1.1) versus 20 (0.97) µg/dL, pre-strike BLL 44 (1.2) versus 49 (1.71) µg/dL, post-strike BLL 31 (1.3) versus 33 (1.20) µg/dL). BLL, blood lead level; µg/dL, micrograms per deciliter

The average difference between measured and predicted post-strike BLL is 0.9 µg/dL, with a standard error of 0.9 µg/dL, shown at the bottom of Table A-2. This indicates that the adjusted core model predicts BLLs nine months after the end of workplace exposure

0.9 µg/dL lower than the average BLLs observed in the ASARCO cohort. Figure A-1 shows the relationship between the observed and predicted BLLs.

Figure A-1: Measured versus predicted BLL (adjusted core model)[1]



[1] ASARCO data versus predictions from final adjustments to core model parameters; BLL, blood lead level; µg/dL, micrograms per deciliter

A linear regression of modeled versus measured BLLs using the nonlinear Leggett model with Leggett's suggested values for RBC saturation estimated a slope of 1.19, meaning that 1.19 x predicted BLL= measured BLL. This suggests a significant (>10%) systematic under-prediction error. In contrast, a linear regression of modeled versus measured BLLs once parameters were adjusted to produce a better fit to the ASARCO post-strike BLLs, produced a slope of 1.02 when the intercept was forced through zero. This means that 1.02 x predicted BLL = measured BLL. This level of systematic error is not significant (<5%).

Test 2: Model performance vs. job tenure

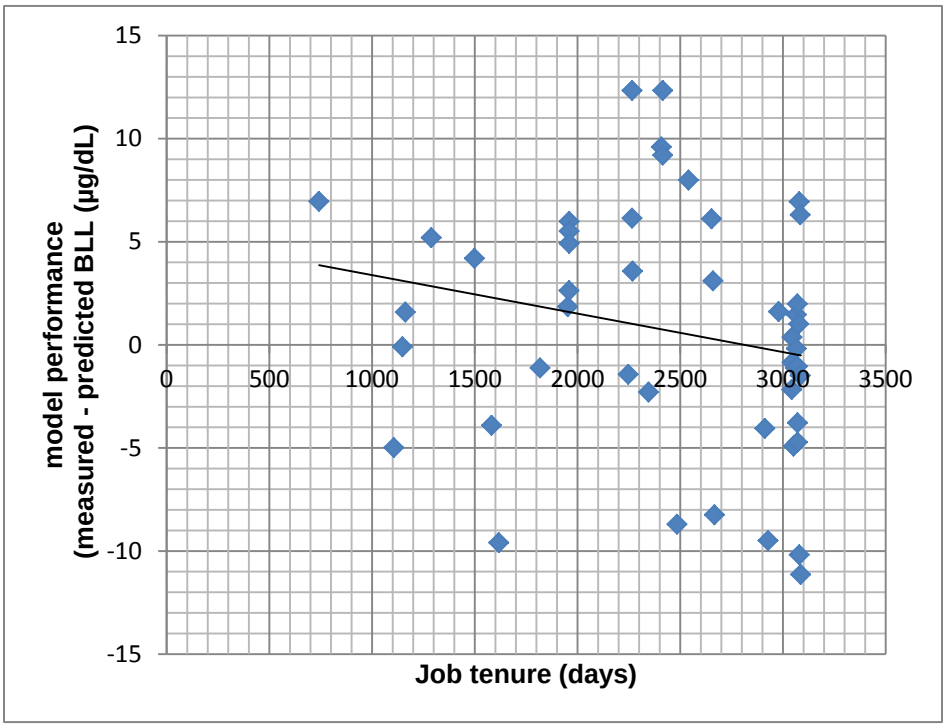
The regression equation analyzing model performance vs. job tenure for our final adjustment to model parameters is:

Eq. (A-2): Model performance (measured – predicted BLL)
= 5.25 – 0.00187 x (days job tenure)

The intercept value of 5.25 has a p-value = 0.11 (LCL, -1.23, UCL, 11.7), and the slope of 0.00187 has a p-value = 0.15 (LCL, -0.004, UCL, 0.0007).

This final equation suggested that differences in measured – predicted BLLs would not be expected to fall outside the deviations observed within the worker cohort at any reasonable length of job tenure as can be seen in Figure A-2 below.

Figure A-2: Model performance versus job tenure[1]



[1]BLL, blood lead level; µg/dL, micrograms per deciliter

This test of consistent model performance regardless of job tenure provided further evidence that the basic structure and exchange ranges for the relatively long-lived compartments in bone and some soft tissues are performing reasonably well.

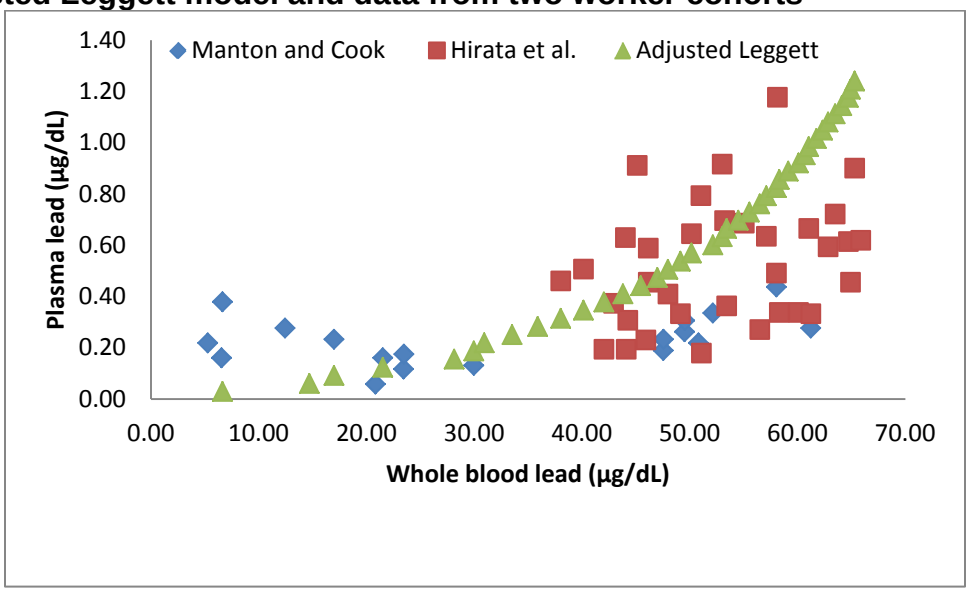
Test 3: Model performance relative to measured bone lead levels in a smelter worker

For the smelter worker who was the subject of our test, Leggett's linear model predicted cortical and trabecular bone concentrations of 44.7 and 27.7 µg/g, respectively, compared to cortical and trabecular bone concentrations of 60 and 160 µg/g predicted by our adjusted model. Corresponding measurements taken from the subject's tibia (cortical) and heel (trabecular) bone were 74 (±8) and 156 (±7), respectively. After estimating intake from the blood lead profile taken from Figure 3 in Nie et al. (2005), measured trabecular bone is very similar to predictions from our adjusted model for this subject. In addition, the ratio of lead levels in trabecular compared to cortical bone is about two to one for all nine retired lead smelter workers in Table 1 in Nie et al. (2005). Though limited, these findings lend further support that the adjusted model provides reasonably accurate predictions of bone lead in chronically exposed workers.

Test 4: Predicted versus measured plasma and urine lead concentrations relative to whole blood lead concentrations in three worker cohorts

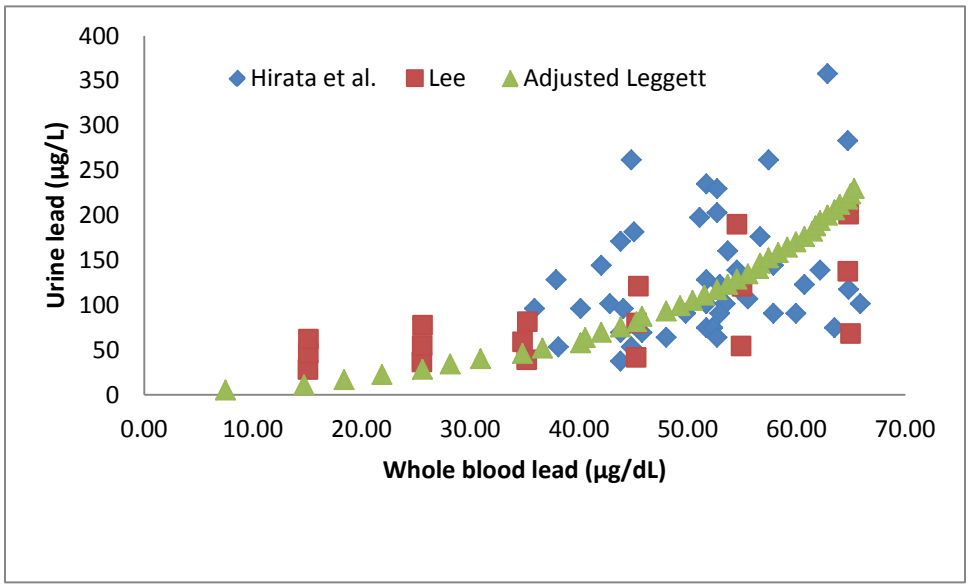
Figures A-3 and A-4 show the model predictions for plasma and urine lead levels compared to measured levels in the three cohorts of workers chronically exposed to lead.

Figure A-3: Plasma lead versus whole blood lead concentration - predictions from the adjusted Leggett model and data from two worker cohorts[1]



[1]The values that appear in Figure A-3 were abstracted using GetData™ given that tabular data for individual subjects were not published in Manton and Cook (1984) or in Hirata et al. (1995). Although the full range of data was visible in the published graph, not all data points were extractable; BLL µg/dL, blood lead level in micrograms per deciliter

Figure A-4: Urine lead versus whole blood lead concentration - predictions from the adjusted Leggett model and data from two worker cohorts[1]



[1]The values from Lee (1982) that appear in Figure A-4 were abstracted using GetData™ and represent the mean for a given BLL ± one standard deviation. Tabular data for individual subjects were not published in Lee (1982); BLL µg/dL, blood lead level in micrograms per deciliter

Notice that the predictions from the adjusted core model for the concentration of plasma lead relative to whole blood lead fall within those reported by Hirata et al. (1995) and Manton and Cook (1984). The predictions for concentration of lead in urine relative to whole blood lead also fall within those reported by Hirata et al. (1995) and Lee (1982).

The consistency of predicted whole blood lead concentration relative to plasma lead and urine lead, to relationships observed in worker cohorts increases our confidence that the final values we selected for RBC saturation and urinary clearance are reasonable.

Test 5: Comparison of modeled tissue lead distributions to measured postmortem lead distributions

Table A-3 presents predicted tissue distributions compared to the reported reference ranges. Note that the proportions of lead distributed to various tissues by the final adjusted Leggett model continue to fall within the range of proportions observed in autopsy studies and those predicted by original Leggett model.

This suggests that our adjustments to bone, blood, and urine parameters did not significantly affect the way the model predicts how lead distributes to other key tissue compartments (e.g., brain and liver) at lower levels of intake (20 µg/day).

Table A-3: Distribution of Lead in Various Tissues - Postmortem Data, Original Model Prediction, Adjusted Model Prediction[1]

	Age 20s – 30s	Age 40s – 50s
Bone (%)		
Postmortem data	0.75 – 0.90	0.85 – 0.95
Original model prediction	0.88	0.90
Adjusted model prediction	0.86	0.88
Blood (%)		
Postmortem data	0.02 – 0.04	0.008 – 0.02
Original model prediction	0.03	0.02
Adjusted model prediction	0.03	0.02
Liver (%)		
Postmortem data	0.03 – 0.07	0.02 – 0.04
Original model prediction	0.04	0.03
Adjusted model prediction	0.04	0.04
Kidneys (%)		
Postmortem data	0.003 – 0.007	0.002 – 0.004
Original model prediction	0.004	0.003
Adjusted model prediction	0.003	0.002
Brain (%)		
Postmortem data	0.002 – 0.004	0.0008 – 0.002
Original model prediction	0.002	0.002
Adjusted model prediction	0.003	0.002
Other tissue (%)		
Postmortem data	0.04 – 0.15	0.02 – 0.08
Original model prediction	0.05	0.05
Adjusted model prediction	0.07	0.05

[1]Exposure scenario: 20 µg/day uptake

A.5 Conclusion

In this appendix, we explained our basis for selecting, adjusting, and checking the nonlinear Leggett model for this task.

An initial review of the literature on lead pharmacokinetics and existing models informed us that nonlinear kinetics would be an important part of any model we used to predict BLLs from chronic occupational exposures at levels of interest to CDPH-OLPPP. In addition, we learned from efforts by others to improve the predictive ability of the two most recent models (Leggett, O'Flaherty) as new data on chronically exposed workers have become available. We reviewed and selected data from five lead worker cohorts (including smelter workers, battery factory workers, lead glass-based paint factory workers, and lead workers from undisclosed settings), as well as autopsy data from the general population, to check how well the model predicted blood and other tissue lead levels resulting from chronic exposures in the range of interest to CDPH-OLPPP.

The model significantly under-predicted worker BLLs when applying Leggett's suggested parameters. Therefore, we needed to adjust bone, urine clearance, and blood parameters in combination to improve the fit of the model to observed data. Multiple tests were needed to ensure that predictions in the range of BLLs of interest to CDPH-OLPPP from the adjusted model compared well to tissue lead levels taken from workers and the general population. With the data available to us we were able to check and verify that:

- The slope of predicted/measured blood lead is near one (test of bias).
- The slope of model performance/job tenure is not significantly different from zero (test of association with job tenure).
- Plasma/whole blood ratios are consistent with data from worker cohorts.
- Trabecular/cortical bone ratios are reasonable when compared to worker data.
- Tissue/body burden ratios are reasonable when compared to autopsy data.

Briefly, OEHHA adjusted urine, bone, and blood parameters in the nonlinear Leggett model to eliminate the under-prediction of BLLs in the ASARCO cohort and achieve predictions comparable to data collected on separate tissue groups from lead workers

and the general population. Our adjustments reduced the under-prediction of BLLs after a nine-month strike among chronically exposed smelter workers from 23% to 2%. The adjusted model maintained reasonable tissue distribution ratios (plasma/whole blood, urine/whole blood, trabecular/cortical bone, tissue/body burden) observed in lead workers and the general population. Finally, the adjusted model performed reasonably well regardless of length of job tenure among chronically exposed workers. Although no model is perfect, our review, selection, adjustments, and checks of model performance provide confidence that the adjusted Leggett model is the best available model for the purposes established in the Scope of Work and that our primary objectives for this part of the project have been met.

B Appendix: OEHHA Modifications to the Adjusted Core Model to Accommodate Workplace Exposure in Leggett+ Model

In Appendix B, we first describe the exposure features (exposure module) added to the adjusted nonlinear form of the Leggett model (core module) and OEHHA's approach to simulating worker lead intake. Then we present our derivation of a default coefficient for the transfer of inhaled lead to blood among workers, including our rationale and assumptions. Finally, we compare predictions from Leggett+ (combined core and exposure modules) with observations from a controlled inhalation chamber study and an occupational field study that reported both airborne exposure and BLLs at the individual level under specific exposure conditions.

B.1 Description of exposure features added to the nonlinear Leggett model

The original Leggett model was a general model not specifically designed to address workplace exposure scenarios. Therefore, OEHHA needed to add a workplace exposure component to the nonlinear form of the Leggett model that we described in Appendix A of this report. The new model is renamed "Leggett+". The exposure component includes features that address both workplace inhalation exposure and the background exposure from inhalation of ambient (non-workplace) air and dietary intake.

B.1.1 Breathing rate

The exposure module includes three different breathing rates to represent activity during work and non-work hours of each day. Simulations involving chronic exposure to workplace airborne lead include work time apportioned as 8 hours/day x 250 days/year. Background exposure includes intake from inhaled air during the other 16 hours per day and time off on weekends and during vacation in each year as well as background dietary intake (See Table 1).

We calculated a time-weighted average breathing rate (BR) of 26 m^3/day based on minute volumes for adult males (OEHHA, 2012a). This BR reflects 10 hours of

moderate activity during the day (30 L/minute = 18.4 m^3/ 8-hr workday + 2 hr off the job), 6 hours of light activity (13.9 L/minute = 5.0 m^3/ 6-hr), and 8 hours of sedentary (5.9 L/minute = 2.8 m^3/ 8-hr) activity off the job.

B.1.2 Inhalation transfer coefficient

OEHHA's task is to model BLL resulting from inhalation exposure to a constant workplace air lead level. Therefore, we need to determine how much of the lead in the air a worker breathes is transferred to his or her blood. The rate and amount transferred to blood depends on several factors including the amount, size, and solubility of deposited particles and their location in the upper and lower respiratory tract. In turn, the location where particle deposition occurs depends on both particle size and a worker's breathing rate. Finally, transfer depends on the conditions in the gut for those particles that deposit in the upper airways and are swallowed.

The chemical form of inhaled lead affects its solubility and therefore influences its absorption from the respiratory tract and gut. Some lead forms (e.g., lead acetate, lead chloride) are soluble in water; other forms (e.g., lead sulfide) are much less soluble (NTP 2011). For the purposes of developing a coefficient for the transfer of inhaled lead to blood, OEHHA chose to make the cautious assumption that lead is inhaled in a highly soluble form and readily absorbed in the lungs and gut, thus making deposition in the lungs based on particle size the critical factor in transfer to blood.

Generally, smaller particles will deposit deeper in the lung (alveolar region), while coarser particles tend to be deposited in the head and ciliated regions where they are cleared by ciliary action or secretions and swallowed (Castellino et al. 1995). Very small particles are more likely to be exhaled. We assume inhaled lead particles deposited in the alveoli are highly soluble in water and hence absorbed to the blood rapidly (within a day) with essentially 100% efficiency (Holgate et al. 1999; Stellman 1998), while particles deposited in the head and ciliated regions of the lung are cleared to the gut where they are absorbed with less efficiency. As the distribution of particles shifts towards coarser particles, more mass is retained in the upper airways, removed and

swallowed, and the amount of lead transferred to the blood via the gut becomes greater for a given air concentration of lead.

The size distribution of airborne lead particles depends on the industrial processes that generate the particles in the first place. Some information is available in the published literature on particle size from studies of different types of industrial operations and construction tasks (Park and Paik 2002; Liu et al. 1996; Spear et al. 1998b; Tsai et al. 1997; Froines et al. 1986; Hinds 1982; Hodgkins et al. 1991a; Hodgkins et al. 1991b; Virji et al. 2009). Hot operations such as found in brass foundries and burning during bridge repair generate smoke and fume (Liu et al. 1996; Spear et al. 1998b; Vork 2003). Workers in mechanical processes, such as cutting, grinding, grid-casting, pasting, and cast-on-strap unloading, have lead exposure composed predominantly of coarser particles (larger than 10 µm) (Liu et al. 1996).

Incorporating varying particle size distributions into the model, however, is impractical for a number of reasons. First, only limited information is available on the wide variety of lead operations and processes because particle size information is not routinely collected in industrial hygiene monitoring surveys. Second, even if it were available, assuming that a particular particle size distribution would be widely applicable across an industry type does not appear to be valid. Different facilities in an industry group (e.g., battery manufacturers) could have different processes or facility layouts. Furthermore, often many operations in a facility use lead and generate different particle size distributions. In these facilities worker exposure will likely be mixed and can vary depending on the location of the worker. Finally, occupational lead regulations must apply across general and construction industries rather than to particular industries, processes, or operations.

If it is impractical to include varying particle size distributions into the model, how should particle size distribution be handled?

In the 1978 lead standard, Federal OSHA addressed the issue by assuming that at air lead concentrations up to 12.5 µg/m^3 all particles are small and 37% of the inhaled lead mass is absorbed to the blood; above this cut point, all particles are large and 8% of the

inhaled lead mass is absorbed to the blood. This assumption, called Assumption C, has been challenged by Froines and others (Froines et al. 1995; Liu et al.1996). While some studies have shown that when lead concentrations are high in the workplace particle size distribution tends to be coarser (Alexander et al. 1999; Inskip and Hutton 1987; Jacko and Overmyer 1979; Park and Paik 2002; Spear et al. 1998b; Tsai et al. 1997), there are processes that generate high concentrations of smaller particles in small spaces (e.g., hot processes like torch cutting on bridges [Vork 2003]). We find there is no basis for assuming a global relationship between mass measurements in the air ($\mu g/m^3$) and particle size distribution (µm) as Federal OSHA did in 1978. If such a relationship existed, then particle size could be inferred by mass measurements and absorption adjusted accordingly.

The original Leggett model has a default assumption that 37% of the lead inhaled is cleared from the respiratory system by either direct absorption or mechanically removed by the ciliary escalator and swallowed. Implied in this assumption is that the other 63% is exhaled. Of the 37%, 95% is retained in the alveoli and absorbed directly to the blood with 100% efficiency. The other 5% is cleared to the gut. The model assumes that 15% of the lead that enters the small intestine is absorbed into the blood. OEHHA agrees with Leggett's assertion that this default assumption is not valid for industrial exposures. Leggett based these assumptions on studies of motor vehicle exhaust in which particle size is in the submicron range where there appears to be little ciliary clearance of deposited lead. In contrast, in studies of particle size distribution in lead industries, particles tend to be much larger and therefore expected to deposit in the upper regions of the respiratory tract where more ciliary clearance of deposited lead is expected. Leggett acknowledged that greater ciliary clearance may be expected in industrial exposures where aerosol particles are often larger.

Having concluded that neither Assumption C nor Leggett's default assumption was valid for our purposes, we decided that an alternative approach based on the important factors involved in the transfer of inhaled particles to blood mentioned above was needed. OEHHA's approach is based on: 1) published particle size distribution data from a variety of workplaces with differing operations that generate a range of particle

sizes (fine to coarse); and 2) a recently developed model for predicting head and lung deposition and clearance based on particle size distributions and other parameters. In our derivation of a default coefficient for the transfer of inhaled lead to blood in workers, presented below, we have made no attempt to address nose blowing as a pathway for clearing lead particles from the head region (Smith et al. 2011).

B.2 Methods for deriving a coefficient for the transfer of inhaled lead to blood in workers

Briefly, OEHHA reviewed the literature to identify studies that provided data on particle size distribution from actual workplaces and selected Park and Paik (2002) and Liu et al. (1996) for evaluation. These studies provide particle size distribution data from 14 industrial workplaces and five different industries with a range of particle sizes. To evaluate the effect of chemical speciation on deposition, we also selected Spear et al.'s (1998a) assessment of particle size distributions in personal breathing zone samples of workers at a primary smelter (Spear et al. 1998b). Next, we looked at two available models for estimating the percent of lead inhaled in the workplace that is deposited in the three regions of the respiratory tract (head, upper, and lower airways). The models we reviewed are the ICRP Human Respiratory Tract Model for Radiological Protection (ICRP 1994) and the more recent MPPD2 (ARA 2012). We selected MPPD2 for our analysis. Finally, we calculated the percentage of inhaled lead transferred to the blood of an exposed worker according to Equation B-1 (see section B.3.3.1).

B.2.1 Studies selected for analysis

Park and Paik (2002) evaluated exposure to airborne lead particles for 117 workers in four types of lead-related industries located in Korea. The particle sizes were measured using personal sampling cascade impactors. Two secondary lead smelting plants, three radiator manufacturing plants, four lead-acid battery manufacturing plants, and three lead powder manufacturing plants were studied. In addition to air samples, whole blood samples were taken on each worker. For each type of industry, the authors reported MMAD, PbA, average respirable fraction, and fraction of particles less than 1 µm aerodynamic diameter (AD).

Liu et al. (1996) reported on the size distributions of lead aerosol from personal samples of workers exposed in a brass foundry and a battery manufacturing plant. Workers were involved in one or more of eight operations during sampling periods. Ninety-four cascade impactor samples were collected over a one-year period. Mean respirable, thoracic, and inhalable fractions (as defined by ACGIH 1994-1995) along with their arithmetic standard deviations were reported for four work areas each in the brass foundry and battery plant.

Spear et al. (1998b) evaluated 46 personal inhalable dust samples taken from workers in a primary lead smelter located in the United States. Samples were obtained from four work areas: ore storage area, sinter plant, blast furnace area, and drossing area. Results were reported as MMAD and range as well as median and mean of the inhalable, thoracic, and respirable fraction. In a companion paper, Spear et al. (1998a) evaluated the chemical speciation of lead dust associated with primary lead smelting using X-ray diffraction analysis. This paper reported the percent total lead sequentially extracted from bulk dust generated by the smelter process.

B.2.2 Lead particle dosimetry using the MPPD2 model

The original MPPD model was developed by the Chemical Industry Institute of Toxicology (CIIT) Center for Health Research; the National Institute of Public Health and the Environment, The Netherlands (RIVM); and the National Institute for Occupational Safety and Health (NIOSH) (Anjilvel and Asgharian 1995; ARA 2012; RIVM 2002).

The MPPD model can be used to predict the deposition of particles between 0.01 and 20 µm in diameter in humans and rats. The model calculates deposition in the lung by the mechanisms of impaction, sedimentation, and diffusion. Despite interspecies differences in lung geometries, the same mathematical formulations are used for both species. The extra-thoracic particle deposition efficiencies used in the MPPD model were adopted from the ICRP (1994) Human Lung Model. Model input parameters include airway morphology, particle properties (size distribution, density, and concentration), and breathing conditions (tidal volume, breathing frequency, and mode, i.e., oral, nasal, or both). In addition, the human model provides parameters for age-

specific modeling of infants and children. The model uses average exposure concentrations and breathing rates to estimate particle depositions over discrete time periods, i.e., temporal variations are not considered. In addition to deposition it also calculates retention of deposited particles as a function of time since particles are removed by mechanical (ciliary) action. The MPPD model has been extensively reviewed by U.S.EPA National Center for Environmental Assessment staff and found useful for rat to human extrapolation in risk assessment (Brown et al. 2005).

For comparison, the previous primary model for estimating particle deposition in humans is the ICRP Human Respiratory Tract Model for Radiological Protection (ICRP 1994). This model provides tabular deposition estimates for 19 activity median aerodynamic diameters (AMADs) (µm), seven lung regions, three modes of breathing, four breathing rates, five age groups, and both sexes. No provision is made for particle size distribution, density, or concentration. The ICRP model has also been formulated as a *Mathematica* package by Guillermo Sanchez (Humorap 1.1) with functions to solve compartmental models with constant fractional rates (http://web.usal.es/~guillermo/publications/Proceedings/IRPA11Biokmod.pdf). It calculates the retention of particles as a function of time in the respiratory and gastrointestinal tracts of individuals resulting from intake of airborne particles (http://web.usal.es/~guillermo/biokmod/mathjournal.pdf). This model package is quite complex and computationally intensive.

In short, there is no currently extant model comparable to the Multi-Path Particle Dosimetry Model (MPPD and subsequent versions) in terms of public availability, complexity, flexibility, and utility for assessing airway particle deposition and retention in the context of human risk assessment. OEHHA used the MPPD2 model extensively in the recently completed “Nickel Reference Exposure Levels” (OEHHA 2012b). In our estimates of lead particle depositions with the MPPD2 model we used the adult Yeh and Schum symmetric lung morphology with normal oronasal augmentation breathing mode (Yeh and Schum 1980).

B.3 Results

Below we present the results of the dosimetry analysis using the MPPD2 model as well as our analyses to check the reliability of the MPPD2 outputs. Finally, we demonstrate that the MPPD2 model outputs compare well to the results from the ICRP Lung Model found in publication 66 (ICRP 1994).

B.3.1 Dosimetry results from MPPD2

We extracted the data from Park and Paik (2002) for air lead concentration and particle size in smelting, radiator manufacturing, battery manufacturing, and lead powder manufacturing settings (Table B-1). Air concentrations ranged from means of 26 to 1084 µg/m^3, with a grand arithmetic mean of 641 µg/m^3. Particle sizes ranged from a MMAD of 1.3 µm to 15.1 µm, with a MMAD of 5.8 µm across all 117 workers. GSDs ranged from 1.5 to 9.6, with a combined GSD of 6.3. Since Park and Paik did not analyze the chemical form of particles, we assumed that the particles in this study were composed of inorganic lead, density 11.34 g/cm^3.

Table B-1: Airborne lead concentration and particle mass median aerodynamic diameter from Park and Paik (2002)[1]

Parameter/Occupational setting	Secondary Smelting, N = 6	Radiator Mfg. N = 42	Battery Mfg. N = 44	Lead Powder Mfg. N = 25	Combined N = 117
AM ± SD Concentration µg/m^3	653 ± 356	26 ± 27	1084 ± 1828	895 ± 1501	641 ± 1391
MMAD µm	4.9	1.3	14.1	15.1	5.8
GSD	5.0	9.6	1.5	1.7	6.3
Density, g/cm^3	11.34	11.34	11.34	11.34	11.34

[1]N, number of samples; AM, arithmetic mean; SD, standard deviation; MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation; Weighted averages of columns 2-5; µm, micrometer; g/cm^3, grams per cubic centimeter

Using the MPPD2 model and data from Park and Paik above, we predicted head and lung deposition fractions for all four occupational settings and five different activity levels

(resting, sitting, light work, moderate and heavy work) (Table B-2). The predicted alveolar depositions ranged from 0.21 to 14.7% for the different occupational settings/activity levels with an arithmetic mean of 9.4% for low physical activity (resting) and an arithmetic mean of 7.8% for high physical activity (heavy work).

Table B-2: Lung dosimetry analysis of occupational airborne lead exposure by the MPPD2 model: multiple activity levels (data of Park and Paik 2002)[1]

Parameter/Occupational setting	Secondary Smelting N = 6	Radiator workers N = 42	Battery workers N = 44	Pb Powder workers N = 25	Combined N = 117
Resting					
Breathing cycle, (cycles/min)	12	12	12	12	12
Tidal volume, mL	625	625	625	625	625
NP dead space, mL	50	50	50	50	50
Output (%)					
Total deposition	0.756	0.743	0.997	0.996	0.760
Total head deposition	0.612	0.520	0.971	0.996	0.617
Airway deposition (TB + Alv)	0.143	0.223	0.026	0.030	0.143
Alveolar deposition (Alv)	0.093	0.117	0.006	0.009	0.094
Sitting					
Breathing cycle, cycles/min	12	12	12	12	12
Tidal volume, mL	750	750	750	750	750
Output (%)					
Total deposition	0.776	0.755	0.998	0.997	0.780
Total head deposition	0.627	0.527	0.975	0.971	0.631
Airway deposition (TB + Alv)	0.149	0.229	0.022	0.026	0.150
Alveolar deposition (Alv)	0.103	0.130	0.006	0.009	0.103
Light work					
Breathing cycle, cycles/min	20	20	20	20	20
Tidal volume, mL	1250	1250	1250	1250	1250
Output (%)					
Total deposition	0.846	0.745	0.999	0.998	0.851
Total head deposition	0.744	0.559	0.992	0.990	0.746
Airway deposition (TB + Alv)	0.102	0.186	0.007	0.008	0.105
Alveolar deposition (Alv)	0.072	0.116	0.002	0.003	0.075
Moderate work					
Breathing cycle, cycles/min	23	23	23	23	23
Tidal volume, mL	1586	1586	1586	1586	1586
Output (%)					
Total deposition	0.750	0.717	0.993	0.991	0.756
Total head deposition	0.605	0.426	0.890	0.891	0.623
Airway deposition (TB + Alv)	0.145	0.291	0.103	0.101	0.133
Alveolar deposition (Alv)	0.082	0.147	0.010	0.013	0.085
Heavy work					
Breathing cycle, cycles/min	26	26	26	26	26
Tidal volume, mL	1920	1920	1920	1920	1920
Output (%)					
Total deposition	0.744	0.711	0.994	0.992	0.750
Total head deposition	0.609	0.421	0.897	0.897	0.625
Airway deposition (TB + Alv)	0.135	0.290	0.097	0.095	0.125
Alveolar deposition (Alv)	0.075	0.125	0.006	0.009	0.078

[1] Number of samples; breathing cycles and tidal volumes for all activity levels from ICRP 1994; cycles/min; normal oronasal augmentor; NP dead space remains the same for all activity levels; NP, naso-pharynx; TB, tracheobronchial deposition fraction; Alv, Alveolar deposition; [5]Deposition and clearance modes in the MPPD2 model refer to fraction deposited on lung surfaces and subsequently cleared through absorption and removal by ciliary action (see text); mL, mililiter

Using the Park and Paik data for heavy work activity (26 cycles/min x 1920 mL tidal volume), for example, the total deposition for the combined group was 75%; the total

head deposition, 62.5%; total airway deposition (tracheobronchial plus alveolar), 12.5%; and alveolar deposition, 7.8%. However, for battery and lead powder workers, nearly 100% of the particles inhaled (14.1 μm and 15.1 μm MMAD, respectively) are deposited compared to nearly 75% for secondary smelting and radiator workers (4.9 μm and 1.3 μm MMAD, respectively). Battery workers have a much higher total deposition because larger particles tend to deposit on respiratory mucosa, while very small particles can behave somewhat like a gas and therefore are partially exhaled. So even though battery workers have a very small fraction getting to the alveoli, almost nothing is exhaled.

In order to check that the MPPD2 model with Park and Paik data was producing reliable results, we conducted several additional analyses: 1) we ran the model in deposition and clearance mode to verify that it produced expected results; 2) we conducted an analysis using different chemical species of lead (Spear et al. 1998a); 3) we conducted analyses using two additional data sets (Liu et al. 1996; Spear et al. 1998b); and 4) we compared the results of the MPPD2 model to particle deposition predictions from the ICRP Human Lung Model, which has been the key reference work in this area for nearly 20 years. These analyses are described below.

Running the model in deposition and mechanical clearance mode showed that a five-day tracheobronchial deposition of lead in radiator workers (26 $\mu g/m^3$, MMAD 1.3 μm, GSD 9.6) was rapidly cleared by the seventh day. By contrast, alveolar deposition was very slowly mechanically cleared (< 3% in nine days) (data not shown).

To evaluate whether differences in lead chemical species, and therefore density, would have a significant influence on deposition, we conducted an analysis using the chemical speciation data from Spear et al. (1998a) for PbO (9.6 g/cm^3), PbS (7.6 g/cm^3), and $PbSO_4$ (6.3 g/cm^3) at a low breathing cycles/minute and constant concentration. The differences were not dramatic (Table B-3). For example, there were no significant differences in alveolar deposition fraction between species of lead among battery or lead powder workers.

Table B-3: Lung dosimetry analysis of occupational airborne lead exposure by the MPPD2 model with different speciation assumptions[1]

Parameter/Occupational setting	Secondary Smelting N = 6	Radiator workers N = 42	Battery workers N = 44	Lead Powder workers N = 25
AM ± SD concentration µg/m^3	653 ± 356	26 ± 27	1084 ± 1828	895 ± 1501
MMAD µm	4.9	1.3	14.1	15.1
GSD	5.0	9.6	1.5	1.7
Pb				
Pb, density, g/cm^3	11.34	11.34	11.34	11.34
Total deposition fraction	0.756	0.743	0.997	0.996
Total head deposition fraction	0.612	0.520	0.971	0.996
Airway deposition fraction, TB + Alv	0.143	0.223	0.026	0.030
Alveolar deposition fraction, Alv	0.093	0.117	0.006	0.009
Mass deposition/alveolus, µg	7.83E-11	3.92E-12	8.10E-12	9.77E-12
Mass deposition/macrophage, µg	6.47E-12	3.24E-13	6.69E-13	8.08E-13
PbS				
PbS, density, g/cm^3	7.6	7.6	7.6	7.6
Total deposition fraction	0.748	0.720	0.997	0.996
Total head deposition fraction	0.612	0.512	0.971	0.996
Airway deposition fraction, TB + Alv	0.136	0.208	0.026	0.030
Alveolar deposition fraction, Alv	0.089	0.106	0.006	0.009
Mass deposition/alveolus, µg	7.44E-11	3.56E-12	7.95E-12	9.86E-12
Mass deposition/macrophage, µg	6.15E-12	2.94E-13	6.57E-13	8.15E-13
PbO				
PbO, density g/cm^3	9.64	9.64	9.64	9.64
Total deposition fraction	0.752	0.734	0.997	0.996
Total head deposition fraction	0.612	0.517	0.971	0.996
Airway Deposition fraction, TB + Alv	0.140	0.217	0.026	0.030
Alveolar deposition fraction, Alv	0.091	0.113	0.006	0.009
Mass deposition/alveolus, µg	7.66E-11	3.77E-12	7.891E-12	9.81E-12
Mass deposition/macrophage, µg	6.34E-12	3.12E-13	6.52E-12	8.11E-13
$PbSO_4$				
$PbSO_4$, density g/cm^3	6.29	6.29	6.29	6.29
Total deposition fraction	0.740	0.710	1.0	1.0
Total head deposition fraction	0.610	0.510	0.970	1.0
Airway deposition fraction, TB + Alv	0.130	0.200	0.026	0.030
Alveolar deposition fraction, Alv	0.087	0.100	0.006	0.009
Mass deposition, alveolus, µg	7.3E-11	3.4E-12	8.0E-12	9.9E-12
Mass deposition, macrophage, µg	6.0E-12	2.8E-13	6.6E-13	8.2E-13

[1] MPPD2, Multipath particle deposition model v2; (Park and Paik 2002); (Spear et al. 1998a); TB, tracheobronchial; Alv, alveolar; AM, arithmetic mean; SD, standard deviation; µg/m^3, microgram per cubic meter; µm, micrometer; g/cm^3, gram per cubic centimeter; Pb, inorganic lead; PbS, lead sulfide; PbO, lead oxide; $PbSO_4$, lead sulfate; MMAD, mass median aerodynamic diameter.

In addition to the Park and Paik (2002) data, we analyzed the data of Liu et al. (1996). In this case, we derived truncated distributions (< 12 µm MMAD) based on weighted

means of binned particle size data for airborne lead exposure of brass foundry workers. For four occupational activities of cutting, furnace, grinding, and pouring with adjusted concentrations of 22 to 122 µg/m^3, MMAD of 2.06 to 4.63 µm, SD of 2.08 to 6.51 µm, and a breathing rate of 12 cycles/minute, 625 mL/cycle (resting), we obtained predicted airway depositions (TB + Alv) of 15.3 to 21.0% and alveolar depositions of 7.9 to 12.6% (Table B-4). Despite a more limited analysis, these results are in broad agreement with the analysis of the Park and Paik (2002) data above (Table B-2). The airway and alveolar deposition fractions are 14.3 – 22.3% and 9.3 – 11.7%, respectively, in the Park and Paik analysis for resting activity level in secondary smelting and radiator manufacturing, which have similar MMADs to those in the brass foundry reported in Liu et al. (1996).

Table B-4: Lung dosimetry analysis of occupational airborne lead exposure in brass foundry workers by the MPPD2 model (data of Liu et al. 1996)[1]

Parameter/Occupational setting	Cutting, N = 14	Furnace, N = 13	Grinding, N = 10	Pouring, N = 13
GM, GSD concentration µg/m^3	621 ± 3.2	158 ± 2.4	509 ±3.2	32 ±1.4
Adjusted concentration µg/m^3	122	112	100	22
MMAD µm	4.63	2.06	4.17	2.44
SD µm	2.08	6.51	2.7	6.38
Density, g/cm^3	11.34	11.34	11.34	11.34
Breathing cycle, cycles/min	12.0	12.0	12.0	12.0
Tidal volume, mL	625	625	625	625
NP dead space, mL	50	50	50	50
Total deposition fraction	0.868	0.685	0.882	0.683
Total head deposition fraction	0.688	0.516	0.672	0.530
Airway deposition fraction, TB + Alv	0.180	0.170	0.210	0.153
Alveolar deposition fraction, Alv	0.108	0.085	0.126	0.079
Mass deposition/alveolus, µg	1.70E-11	1.23E-11	1.63E-11	2.24E-12
Mass deposition/macrophage, µg	1.40E-12	1.02E-12	1.35E-12	1.85E-13

[1] MPPD2, Multipath particle deposition model v2; (Liu et al. 1996); data reduced by truncated amount in largest particle size bin (> 10 µm); cycles/min normal oronasal augmenter; GM, geometric mean; GSD, geometric standard deviation

Finally, we examined the sinter plant and blast furnace data from Table 1 in Spear et al. (1998b), for finer particles. Overall, the values obtained by these data (data not shown) were similar to the values from Liu et al. (1996) and Park and Paik (2002).

B.3.2 Dosimetry results from ICRP Human Lung Model publication 66 lookup tables

For comparison, in Table B-5 we have given the particle deposition predictions of the ICRP Human Lung Model (ICRP 1994) for different particle sizes and physical activity levels.

Table B-5: Particle deposition by activity level and particle size by the ICRP Human Lung Model (ICRP 1994)[1]

	size (AMAD)					
Region	**1 µm**	**3 µm**	**5 µm**	**7 µm**	**10 µm**	**15 µm**
0.45 m^3/hr (resting)						
Bronchi	0.016	0.019	0.018	0.016	0.012	0.009
Bronchioles	0.015	0.013	0.010	0.0078	0.005	0.003
Alveoli	0.14	0.14	0.11	0.082	0.056	0.032
Total deposition	0.39	0.67	0.74	0.75	0.74	0.70
0.54 m^3/hr (light activity)						
Bronchi	0.014	0.016	0.015	0.013	0.011	0.007
Bronchioles	0.014	0.011	0.009	0.007	0.004	0.002
Alveoli	0.15	0.14	0.10	0.078	0.052	0.029
Total deposition	0.42	0.69	0.76	0.77	0.75	0.70
1.5 m^3/hr (moderate activity)						
Bronchi	0.008	0.006	0.005	0.004	0.003	0.002
Bronchioles	0.007	0.005	0.004	0.003	0.002	0.001
Alveoli	0.099	0.067	0.045	0.031	0.019	0.010
Total deposition	0.53	0.79	0.83	0.82	0.78	0.72
3.0 m^3/hr (heavy activity)						
Bronchi	0.010	0.016	0.015	0.013	0.010	0.006
Bronchioles	0.009	0.011	0.009	0.007	0.005	0.003
Alveoli	0.12	0.10	0.073	0.053	0.034	0.018
Total deposition	0.42	0.70	0.77	0.77	0.75	0.71

[1]ICRP, International Commission for Radiologic Protection; [2]AMAD, Activity Median Aerodynamic Diameter; µm, microgram; m^3/hr, cubic meters per hour; There is an error in the ICRP Publication 66 deposition tables: AMTD is correct for aerosol sizes 0.0006-0.2 µm, but aerosol sizes 0.5-20 µm actually refer to AMAD (activity median aerodynamic diameter). For a radionuclide, AMAD is equal to MMAD if the radioactivity per unit mass is constant among all particle sizes in the distribution of particle sizes (Leggett 2012 personal communication); Total deposition, including upper airway and extra-thoracic, i.e. the fraction that is not exhaled

The values derived from the ICRP lung model are similar to those derived from MPPD2 regardless of activity level. MMAD ranges from 2 µm to 4.6 µm in the Liu data (Table B-4). Using MPPD2, the total deposition ranges from 68.3% to 88.2% and deposition in

the alveoli 7.9% to 12.6% (Table B-4). This is very similar to the values predicted by the ICRP model for particles in the 3 – 5 µm size range (67% to 74% for total deposition and 11% to 14% for deposition in the alveoli) in Table B-5.

B.3.3 Default inhalation transfer coefficient (ITC)

B.3.3.1 Derivation of ITCs

We determined the percentage of inhaled lead that transfers to the blood according to Equation B-1.

Eq. B-1: Inhalation transfer = (alveolar deposition x lung absorption)
+ (ciliated and head region deposition x average gut absorption)

where:

- Alveolar, ciliated, and head region deposition fractions are based on MPPD2 lung dosimetry analysis (Table B-2).
- Lung absorption in the alveolar region is assumed to be 100%.
- Average gut absorption of lead mechanically removed from the ciliated and head region and swallowed is assumed to be 30%.

We assume a higher gut absorption factor than Leggett's default of 15% because ciliary clearance occurs over days in which three conditions exist when lead enters the gut - after hours of fasting, with liquid between meals, or during meals. The range of gut absorption of lead in mass balance studies is 30 - 70% after several hours of fasting, 8 - 30% with liquid between meals, and 3 - 20% for intake with solids. We estimated mean absorption fractions (AF) for the three conditions as 50%, 19%, and 12%, respectively, by taking the mid-points of the ranges in published studies. (See Appendix A for a brief review of the balance studies that examined the range of absorption fractions under each condition.) We calculated a 24-hr TWA absorption of 30% assuming 10 hours fasting (50% AF), 10 hours with liquids between meals (19% AF), two hours intake with solids (12% AF),and two hours in which no lead is swallowed.

B.3.3.2 Calculation of inhalation transfer coefficients

Below we present a sample inhalation transfer coefficient calculation for secondary smelting, resting activity level.

We assume particles behave as follows based on lung dosimetry analysis using Park and Paik data presented in Table B-2.

- 75.6% of the lead inhaled is deposited in the respiratory tract and 24.4% is exhaled.
- 9.3% of the inhaled mass is deposited in the alveolar region and absorbed to blood.
- 66.3% of the inhaled mass is removed by ciliary action or secretions, swallowed, and deposited in the GI tract (total deposition fraction minus alveolar deposition fraction).

Then, we calculate a grand transfer factor of 29.2% by adding the amount of inhaled mass that is absorbed through the alveolar region of the lung to the mass swallowed and absorbed through the GI tract (9.3% x 100% + 66.3% x 30% = 29.2%).

B.3.3.3 Selection of a default inhalation transfer coefficient

We selected 30% as our default inhalation transfer coefficient after analyzing the data in several different ways. First, using the Park and Paik data and assuming an average BR of 25 L/min during the exposure period, we calculated an ITC for each occupational setting (range 30.1% - 30.5%). Note the ICRP associates a breathing rate of 25 L/min with light activity and U.S. EPA associates breathing rates of 14 and 30 L/min with light and moderate activity, respectively, for adult men. We also calculated transfer coefficients using the Park and Paik data for all four occupational settings and all five ICRP activity levels (Table B-6a). The transfer coefficients ranged from 28% to 32% with a midpoint of 30%. Finally, we calculated a TWA transfer coefficient for each occupational setting using the same activity weighting factors for the 8-hr exposure period as used to derive a 24-hr average breathing rate (33% sedentary, 25% light, 42% moderate) (Table B-6b). The TWAs ranged from 29% - 31%; midpoint 30%.

Table B-6a: Inhalation transfer coefficient (ITC) by worker group and activity level[1]

Activity Level	ITC			
	Secondary smelting	**Radiator manufacturing**	**Battery manufacturing**	**Lead powder manufacturing**
Resting	29%	31%	30%	31%
Sitting	31%	32%	30%	30%
Light work	30%	31%	30%	30%
Moderate work	28%	32%	31%	30%
Heavy work	28%	30%	30%	30%

[1] ITC, inhalation transfer coefficient

Table B-6b: TWA inhalation transfer coefficients (ITC) by occupational setting[1]

Occupational setting	TWA ITC
Secondary smelting	29%
Radiator manufacturing	31%
Battery manufacturing	29%
Lead powder manufacturing	31%

[1]TWA, time weighted average; ITC, inhalation transfer coefficient

Our data indicate that while particle size distribution has a significant impact on the total fraction of inhaled lead deposited in the head and airways and on the fraction deposited in the alveoli, the fraction ultimately transferred to the blood does not vary greatly by particle size distribution. Battery manufacturing and lead powder manufacturing, which tend to have much larger particle sizes (MMAD 14.1µm; 15.1µm) had similar ITCs to smelting and radiator manufacturing, which have much smaller particle sizes (MMAD 4.9 µm; 1.3µm). The decrease in the fraction deposited deep in the lung when particle

sizes are large, is offset by an increase in the total head deposition fraction (larger particles are not exhaled but deposit in the head region) and subsequent swallowing and gut absorption.

In summary, based on actual data on particle size distributions measured in occupational settings, we derived a default coefficient of 30% for the absorption of lead from inhaled particles for use in the exposure portion of the model.

In the next section, we checked to see that simulations from the Leggett+ model adequately predict workplace measurements by comparing model predictions with BLL measurements reported in our selected studies (Griffin et al. 1975; Williams et al. 1969; Snee 1982).

B.4 Methods for assessing the performance of the Leggett+ model

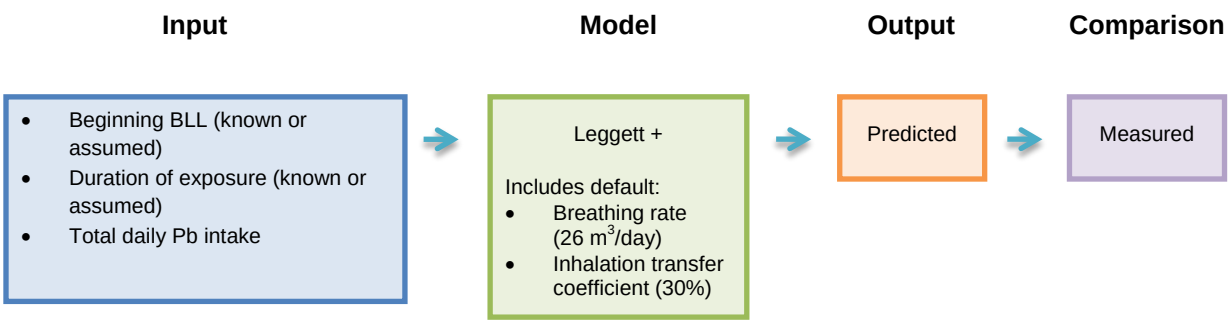
The purpose of the Leggett+ model is to inform changes to the California General Industry and Construction PEL for lead (Cal/OSHA 2007a, 2007b). Therefore, the primary criterion for assessing the Leggett+ model is its predictive validity for exposure scenarios relevant to industrial exposures and therefore of interest to CDPH-OLPPP. An ideal model would predict BLLs in workers exposed during relatively short or long periods to air concentrations in the workplace ranging from < 10 $\mu g/m^3$ to > 200 $\mu g/m^3$ in workplace air.

Because there were no measurements of workplace air lead concentration in the ASARCO dataset, we needed to find additional studies with exposure and blood lead measurements taken at the individual level to evaluate Leggett+ for task one. We found several studies that examined the relationship between personal breathing zone air concentration and BLLs among lead industry workers and others exposed to lead (Griffin et al. 1975; Azar et al. 1975; Chavalitnitikul et al. 1984; Gross 1979, 1981; Hammond et al. 1981; Hodgkins et al. 1991a; Hodgkins et al. 1991b; Hodgkins et al. 1992; Kononen et al. 1989; Rodrigues et al. 2010; Snee 1981, 1982; Williams et al. 1969). From the studies that provided enough individual-level data to help us compare measured BLLs to predicted BLLs from Leggett+, we selected for further analysis two

studies which cover the range of BLLs, workplace air concentrations, and exposure durations of interest to CDPH-OLPPP (Griffin et al. 1975; Williams et al. 1969).

From these two studies we extracted data for each study subject on beginning BLL, ending BLL, total daily lead intake, and duration of exposure. We input the data into the Leggett+ model to get a predicted BLL for each subject. We then compared the predicted BLL to the subject's measured BLL (see Figure B-1). In some cases not all the desired information was available and we were forced to make assumptions. However, at a minimum, studies had to provide individual-level data on continuous personal breathing zone airborne lead concentration (for chamber study) or on-duty personal breathing zone PbA (for workplace study), and ending BLL. Our assumptions are identified and discussed below under each study. See Table B-7 for a summary of model inputs for each study.

Figure B-1: Model validation diagram[1]



[1]BLL, blood lead level; Pb, lead; m^3/day, cubic meters per day

B.4.1 Study and subject selection criteria

In an initial review of the occupational literature, it became clear that many factors, if not adequately controlled in the design of studies measuring air lead levels and worker BLL or during the analysis, could confound the relationship between workplace air concentrations and BLLs among exposed workers (Hodgkins et al. 1991b; Hodgkins et

al. 1992; Kononen et al. 1989). Therefore, we restricted our selection of studies and subjects to those meeting the following criteria:

1) The study needed to report personal air concentration measurements coupled with blood lead measurements.
2) Only studies that reported relatively constant air concentrations over time were selected (i.e., no substantial changes in workplace or controlled chamber conditions).
3) Only studies that collected some information about the level of background exposure, or had information that could be used to make a reasonable assumption about background exposure, were selected.
4) Only subjects exposed at least six hours per day, five days per week, were included.

A chamber study conducted by Griffin et al. (1975) and an occupational study conducted by Williams et al. (Williams et al. 1969; Snee 1982) met our selection criteria.

B.4.2 Data extraction

B.4.2.1 Griffin et al. (1975)

Griffin and co-workers (Griffin et al. 1975) determined changes in BLL with time in 31 healthy adult male volunteers who were exposed to elevated levels of airborne lead concentration for 23 hours/day for about 16 weeks in an environmentally controlled exposure chamber. There were 12 non-exposed control subjects. Two sets of experiments were reported. One experiment exposed subjects to an average airborne lead concentration of 10.9 µg/m^3 in the exposure chamber over the entire exposure period. Another experiment exposed subjects to an average airborne lead concentration of 3.2 µg/m^3 in the exposure chamber over the entire exposure period. BLLs were obtained from each subject in each experiment prior to, during, and after exposure ended.

We removed five subjects with very short-term exposure that is more likely to be influenced by exposure prior to the start of the experiment (i.e., less than 30 days) and

two additional subjects with suspect back-calculated intake during the exposure period (i.e., less than zero relative to pre-exposure intake). The remaining 24 subjects were included in our analysis.

Exposure periods were reported for each participant and varied by subject. The shortest exposure period for those included in our analysis was 42 days. For most subjects the exposure period was about 16 weeks. For modeling purposes we used each individual's reported exposure period.

We extracted the authors' reported baseline BLLs, taken prior to entering the exposure chamber, and end-of-exposure BLLs for each subject.

For modeling purposes we used the reported mean of all daily air lead measurements for the entire exposure period (experiment 1 - 10.9 µg/m^3; experiment 2 - 3.2 µg/m^3).

Lead content in the diets of each subject was analyzed. However, the authors reported individual averages over the entire exposure period without providing subject numbers. Therefore, for modeling purposes we back-calculated the daily uptake of lead (representing the ambient air and dietary lead intake) for each subject from the preexposure BLL

B.4.2.2 Williams et al. (1969)

Williams et al. (1969) collected personal breathing zone air and blood lead concentrations from British battery plant workers exposed during a period of time when older process technology was in use (Hodgkins et al. 1992). Thirty-nine workers were followed. However, Williams et al. believed that 10 of 39 BLL test results were contaminated and threw them out, leaving 29 workers with complete information. Nineteen workers were exposed during three processes with high air concentrations (79 – 298 µg/m^3). Ten workers, comprising the two control groups, were exposed to air concentrations of 8 – 13 µg/m^3. Williams et al. reports that the jobs of the men selected for the study "…did not entail wearing respirators." BLLs ranged from 22.5 – 33.0 µg/dL in the control group and from 44.6 – 93.0 µg/dL in the exposed group (Snee 1982; Williams et al. 1969).

Of the 29 subjects for whom individual data were available on exposure and BLL, as presented in Snee (1982), we selected 16 for model validation. We excluded 13 of the 29 subjects because they had BLLs over 61 µg/dL. BLLs above 60 are less likely to represent current chronic exposure levels and are outside the range of BLLs CDPH-OLPPP asked us to model.

Job tenure was not available for individual subjects. For validation purposes we assumed job tenure of 20 years for all subjects. We based this assumption on data in the Hodgkins et al. (1991) study of battery workers. As reported by Hodgkins et al., the mean seniority of workers in both plants studied was about 20 years.

Pre-exposure BLLs were not available. We assumed that all subjects had a baseline BLL of 20 µg/dL at the start of their employment. The Williams et al. simulation starts in the late 1940s/early 1950s, under the assumption that workers in the study had worked in the plant for 20 years. BLLs among the controls in the Kehoe inhalation studies, started in the 1950s, were around 20 µg/dL. For end-of-exposure BLLs we used the individual's reported BLL in the study.

Time-weighted average lead exposure was available for each subject for on-duty exposures. The air concentrations ranged from 8 – 166 $\mu g/m^3$. We assumed that the air lead concentration reported in the study reasonably represented the subjects' exposure over their job tenure.

Off-duty inhalation and dietary lead exposure were assumed to be represented by the background BLL typical of the 1960's and set at 20 µg/dL (Gross 1979). We back-calculated the uptake of lead from the assumed background BLL of 20 µg/dL.

Table B-7: Model inputs[1]

Study	Griffin et al. (1975)	Williams et al. (1969)
Study type	• Chamber • Prison volunteers	• Occupational • Battery workers in England
Subjects	• Excluded 7 of 31 subjects. o 5 with very short-term exposure o 2 with suspect intake during exposure period • No smoking data reported. • N = 24	• Excluded 23 of 39 workers. o 10 with missing BLL data o 13 with BLLs above 60 µg/dL • No smoking data available. • N = 16
Breathing rate (BR)	• Assumed default BR of 26 m^3/d.	• Assumed default BR of 26 m^3/d.
Exposure duration	• No assumptions made. • Data available for every subject. • Range 4 – 16 w; most 16 w	• Assumed 20 y based on mean seniority of battery workers in another study.
BLL	• No assumptions made. • Beginning and ending BLL available for each subject.	• Assumed beginning BLL of 20 µg/dL based on Kehoe data. • Ending BLL is BLL at time of study.
Inhalation exposure	• No assumptions made. • Monitored 23 h/d. • air lead concentration available for each subject. • Experiment 1: 10.9 µg/m^3 • Experiment 2: 3.2 µg/m^3	• On-duty PbA available for each subject. • Range 8 – 166 µg/m^3 • Assumed the on duty PbA was constant for each subject over job tenure. • Off-duty inhalation and dietary intake back-calculated from assumed background BLL of 20 µg/dL.
Dietary exposure	• No assumptions. • back-calculated as daily uptake	• Off-duty inhalation and dietary intake back-calculated from assumed background BLL of 20 µg/dL.

[1]BLL, blood lead level; µg, microgram; dL, deciliter; N, number; BR, breathing rate; m^3/d, cubic meters per day; w, week; h/d, hour per day; PbA, air concentration of lead

B.5 Results

For each study, OEHHA examined whether the Leggett+ model predicted an accurate BLL from estimates of air concentration and dietary intake for each day during each

subject's exposure period. Table B-8 lists the attributes of subjects from each study along with the BLL predicted from the Leggett+ model.

Table B-8: Measured BLL versus BLL predicted by Leggett+[1]

Subject ID	PbA (µg/m3)	Exposure Period (days)	Total intake (µg/d)	Measured BLL (µg/dL)	Predicted BLL (µg/dL)	Measured less Predicted
Griffin et al. 1975						
32	3.2	123	67.1	30	27.3	2.7
33	3.2	123	61.3	25	25.6	-0.6
34	3.2	123	73.4	28	29.1	-1.1
35	3.2	102	67.1	32	27.1	4.9
37	3.2	53	48.9	18	20	-2
38	3.2	102	46.7	23	20.3	2.7
39	3.2	98	42.6	18	18.6	-0.6
310	3.2	123	61.3	24	25.6	-1.6
311	3.2	120	58.6	27	24.8	2.2
312	3.2	123	64.1	30	26.5	3.5
313	3.2	102	56	26	23.6	2.4
314	3.2	78	67.1	25	26.7	-1.7
317	10.9	123	120.3	32	35	-3
318	10.9	123	123.1	43	35.6	7.4
320	10.9	123	115	36	33.9	2.1
321	10.9	123	135.7	37	38	-1
322	10.9	113	123.1	41	35.3	5.7
323	10.9	123	105.7	30	31.7	-1.7
326	10.9	42	150.7	39	38	1
327	10.9	123	126	39	36.2	2.8
328	10.9	123	123.1	36	35.6	0.4
329	10.9	77	120.3	31	33.6	-2.6
330	10.9	77	115	32	32.4	-0.4
331	10.9	77	103.6	28	29.5	-1.5
Average measured less predicted BLL: 0.83 µg/dL						
Williams et al. 1969						
41	10	7300	41	25.8	26.9	-1.1
42	12	7300	44	27.6	27.8	-0.2
43	9	7300	39	28	26.4	1.6

Subject ID	PbA (µg/m3)	Exposure Period (days)	Total intake (µg/d)	Measured BLL (µg/dL)	Predicted BLL (µg/dL)	Measured less Predicted
44	9	7300	39	28.8	26.4	2.4
45	13	7300	46	29	28.3	0.7
46	13	7300	46	30	28.3	1.7
47	8	7300	38	32.4	25.9	6.5
48	8	7300	38	33	25.9	7.1
49	79	7300	155	44.6	47.3	-2.7
410	166	7300	300	45.6	59.2	-13.6
411	159	7300	288	51.2	58.5	-7.3
412	129	7300	238	56.8	55.1	1.7
413	159	7300	288	59.4	58.5	0.9
414	121	7300	225	61	54	7
428	13	7300	46	22.5	28.3	-5.8
429	8	7300	38	24.6	25.9	-1.3
Average measured less predicted BLL: -0.15 µg/dL						

[1] BLL, blood lead level; ID, indentification number; µg/m3, microgram per cubic meter; µg/d, microgram per day; µg/dL, microgram per deciliter; PbA 24-hr time weighted average (TWA) air concentration of lead in chamber air; for Griffin et al. study. For Williams et al., PbA, on-duty 8-hr TWA. As described in the text, we back-calculated off-duty intake from an assumed background BLL of 20 µg/dL

The difference between measured and predicted BLLs for each study subject is shown in the last column of Table B-8. The average difference between measured and predicted BLL for the Griffin et al. data set is 0.83 µg/dL; the average difference for the Williams et al. data set is - 0.15 µg/dL.

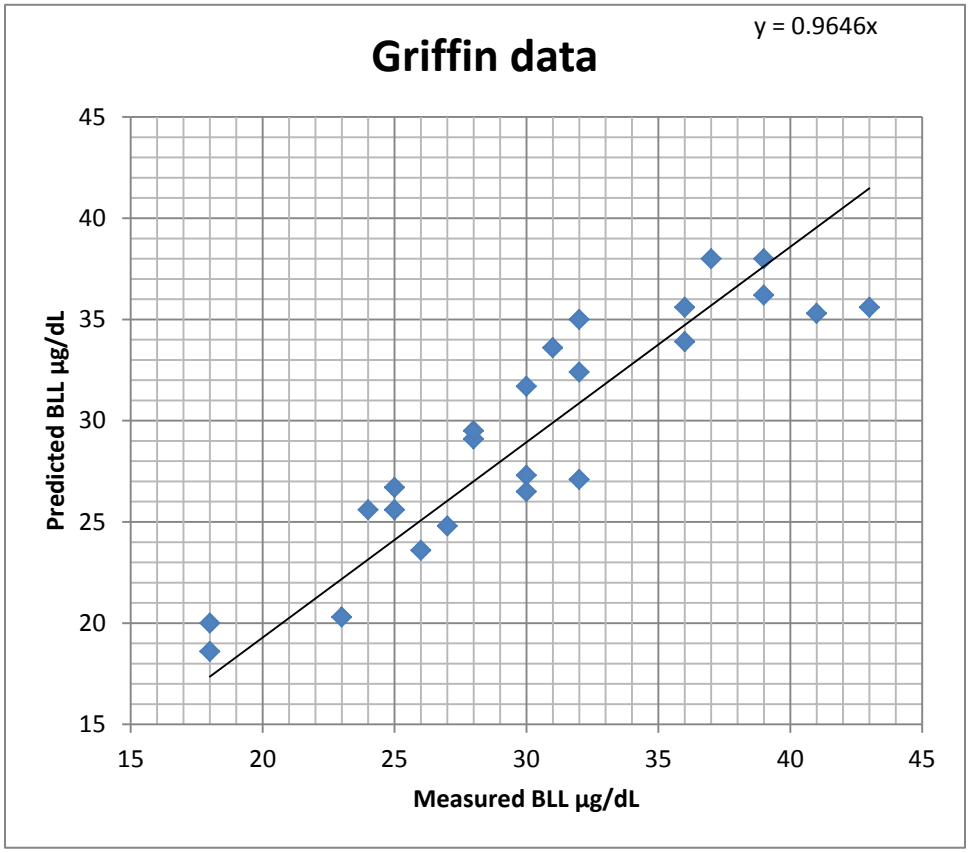
B.5.1 Test 1: Goodness of fit

We checked for systematic bias by conducting a regression analysis of measured versus predicted BLL for both the Griffin et al. and the Williams et al. datasets.

B.5.1.1 Model prediction of Griffin et al. (1975) data

A linear regression of predicted versus measured BLLs from the Griffin study using the Leggett+ model estimated a slope of 0.96 (i.e., 0.96 x measured BLL= predicted BLL), suggesting that there is no evidence of systematic bias (< 10%). The average difference of linear (measured – predicted) intake for this cohort is 0.83 µg/dL. See Figure B-2 below.

Figure B-2: Check for systematic bias – Griffin et al. 1975[1]

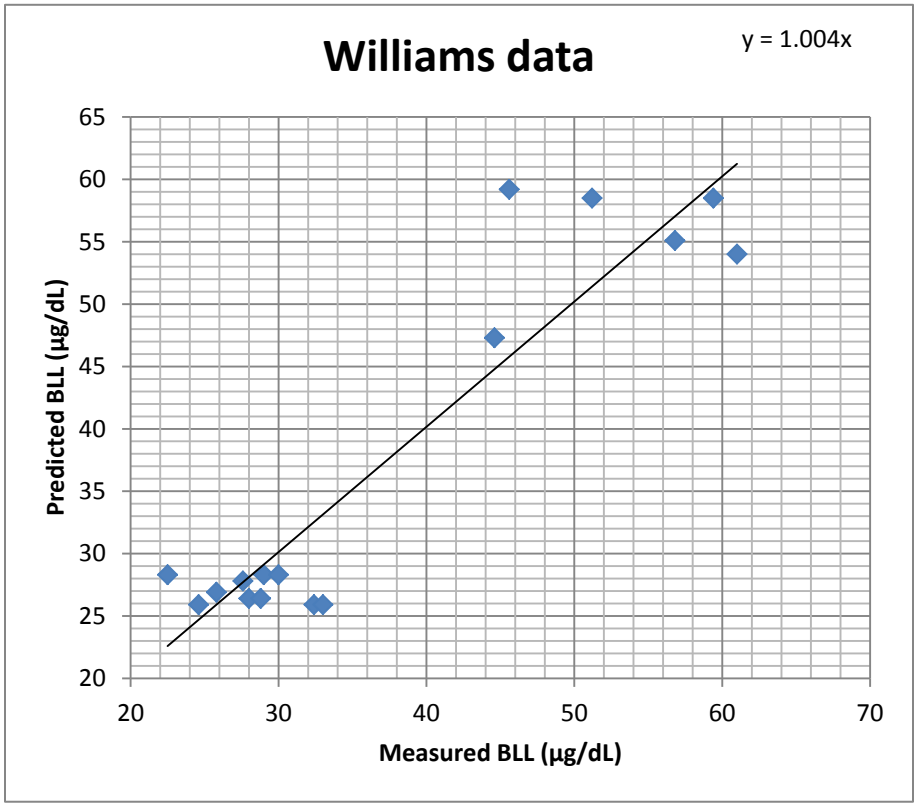


[1] Breathing rate (BR) = 23.5 m^3/day and ITC = 34% to reflect continuous exposure conditions in chamber study; BLL µg/dL, blood lead level in micrograms per deciliter

B.5.1.2 Model prediction of Williams et al. (1969) data

Using Leggett+ model, we performed a linear regression of predicted versus measured BLLs from the Williams study. Our analysis estimated a slope of 1.004, meaning that 1 x measured BLL= predicted BLL, suggesting that there is no evidence of systematic bias (< 10%). The average difference of linear (measured – predicted) intake for this cohort is -0.15 µg/dL. See Figure B-3 below.

Figure B-3: Check for systematic bias – Williams et al. 1969[1]



[1] Breathing rate (BR) = 26 m^3/day and ITC = 30% to reflect occupational scenario; BLL µg/dL, blood lead level in micrograms per deciliter

B.5.2 Test 2: Model performance versus exposure duration

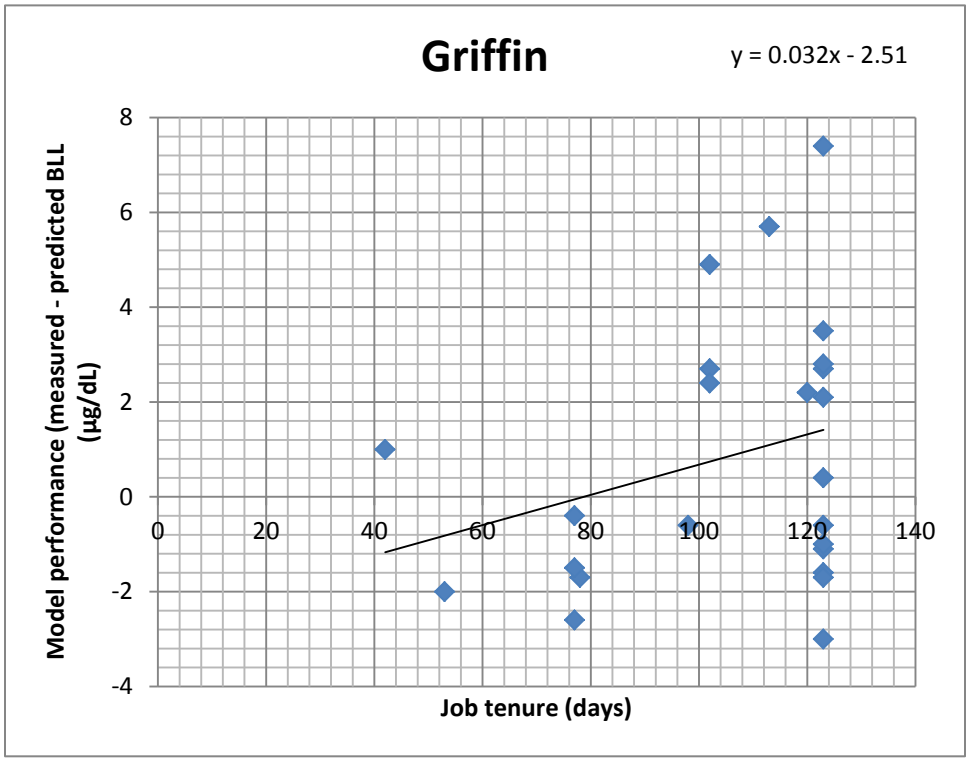
Analysis of model performance versus exposure duration was limited to the Griffin data set. As described earlier, job tenure was not available for workers in the Williams study, and we assumed uniform job tenure for this cohort.

The regression equation analyzing the performance of the Leggett+ model versus job tenure is:

- Model performance (measured – predicted BLL) = -2.5 + 0.032 x (days job tenure), p-value = 0.18
- The intercept value of -2.5 has a p-value = 0.32 (LCL, -7.67, UCL, 2.65), and the slope of 0.032 has a p-value = 0.18 (LCL, -0.02, UCL, 0.08).

This equation suggested that differences in measured – predicted BLLs would not be expected to fall outside the deviations observed within the worker cohort, although the analysis is limited as the longest exposure period was 128 days. See Figure B-4 below.

Figure B-4: Model performance versus exposure duration – Griffin et al. 1975[1]



[1]BLL µg/dL, blood lead level in micrograms per deciliter

B.6 Conclusion

In Appendix A, we tested the adjusted core model and determined that the model predicted valid BLLs after a period of chronic exposure to lead at work followed by an extended period without workplace exposure. In Appendix B, we added an exposure module to the adjusted core model and re-named it the Leggett+ model. Our objectives for this appendix were to check the front-end exposure module and its default settings for breathing rate and inhalation transfercoefficient. We tested the Leggett+ model with data from one chamber and one occupational study. The data used to check model performance include relatively short or long exposure periods and personal breathing zone concentrations in the workplace ranging from < 10 µg/m^3 to > 160 µg/m^3. These studies represented both steady-state exposures from study subjects who either served

many years in the location performing the job where they were monitored, or much shorter-term exposure periods in which the investigator measured blood lead multiple times during the exposure period. These are the conditions expected during workplace exposure and therefore of interest to CDPH-OLPPP.

Our analysis of model performance as described above indicates that our default breathing rate and coefficient for the transfer of inhaled lead to blood are reasonable. Furthermore, this gives us confidence that Leggett+ is ready for modeling workplace air lead concentrations that result in BLLs of interest of CDPH-OLPPP, which in turn will inform CDPH-OLPPP's recommendation for a health-based permissible exposure limit for lead.

C Appendix: Acronyms, symbols and special terms

Acronym/symbol	Definition
<	Less than
>	Greater than
µg	Microgram
µm	Micrometer
ACSL	Advanced Continuous Simulation Language
AD	Aerodynamic diameter
Adjusted core model	The adjusted version of the original nonlinear Leggett model. This part of the model plus a new exposure module is called Leggett+ in this report
AF	Absorption fraction
Alv	Alveolar region of the lung
AM	Arithmetic mean
ASARCO	American Smelting and Refining Company
Biokinetic	Another type of computer model characterizing the transfer, distribution, and elimination of lead in the body
BLL	Blood lead level (whole blood)
BR	Breathing rate
Cal/EPA	California Environmental Protection Agency
Cal/OSHA	Division of Occupational Safety and Health
CDPH-OLPPP	California Department of Public Health, Occupational Lead Poisoning Prevention Program
CIIT	Chemical Industry Institute of Toxicology
cm^2	Centimeter squared
cm^3	Centimeter cubed
dL	Deciliter
EVF	Extra vascular fluid
FORTRAN	Formula Translating System
g	Gram
GI	Gastro-intestinal
GM	Geometric mean
GSD	Geometric standard deviation
GUI	Graphical user interface
Half-life	The half-life or elimination t½ is the time required for the plasma concentration of a chemical to decrease by one-half
ICRP	International Commission for Radiological Protection

Acronym/symbol	Definition
ITC	Inhalation transfer coefficient
LCL	Lower confidence limit
Leggett+	OEHHA enhanced version of the Leggett model for lead
LLI	Lower-lower intestine
ln	Natural log
m^3	Meter cubed
MATLAB	Matrix Laboratory – a proprietary software program for model building and execution
mL	Milliliter
MMAD	Mass median aerodynamic diameter
MPPD	Multipath Particle Dosimetry model
MPPD2	Multipath Particle Dosimetry model version 2
MSE	Mean squared error
NIOSH	National Institute for Occupational Safety and Health
NP	Naso-pharynx region of the respiratory system
OEHHA	Office of Environmental Health Hazard Assessment
Pb	Symbol for lead
PbA	Workplace air concentration of lead if not specified otherwise
PBPK	Physiologically-based Pharmaco-kinetic – refers here to the way a computer model characterizes how lead is taken up, distributed, metabolized, and eliminated in the adult human body
PEL	Permissible Exposure Limit
p-value	Test of statistical significance
R^2	Regression coefficient indicating level of explained variability in the outcome variable
RBC	Red blood cells (erythrocytes)
RIVM	National Institute of Public Health and the Environment, The Netherlands
SD	Standard deviation
SI	Small intestine
t1/2	Half-life of lead in the body, body tissue or body compartment
TB	Tracheobronchial
TWA	Time-weighted average
UCL	Upper confidence limit
ULI	Upper-lower intestine
XRF	X-ray fluorescence

D References

ACGIH (1994-1995), *Threshold limit values for chemical substances and physical agents and biological exposure indices* (Cincinnati, OH: American Conference of Governmental Industrial Hygienists (ACGIH) Technical Affairs Office).

Alexander, W. K., Carpenter, R. L., and Kimmel, E. C. (1999), 'Breathing zone particle size and lead concentration from sanding operations to remove lead based paints', *Drug and chemical toxicology,* 22 (1), 41-56.

Anjilvel, S. and Asgharian, B. (1995), 'A multiple-path model of particle deposition in the rat lung', *Fundamental and applied toxicology : official journal of the Society of Toxicology,* 28 (1), 41-50.

ARA (2012), 'Multiple-Path Particle Dosimetry Model (MPPD v 2.11): A Model for Human and Rat Airway Particle Dosimetry', Applied Research Associates, Inc. (ARA). MPPD2 accessed from (http://www.ara.com/products/mppd.htm).

Ashford, N.A., Gecht, R.D., Hattis, D.B (1977) 'The effects of OSHA medical removal protection on labor costs of selected lead industries', Center for Policy Alternative Massachusetts Institute of Technology, Cambridge, Massachusetts

Azar, A., Snee, R. D., and Habibi, K. (1975), 'An epidemiologic approach to community air lead exposure using personal air samplers', *Environmental quality and safety. Supplement,* 2, 254-90.

Barry, P. S. (1975), 'A comparison of concentrations of lead in human tissues', *British journal of industrial medicine,* 32 (2), 119-39.

Barton, J. C. (1989), 'Retention of radiolead by human erythrocytes in vitro', *Toxicology and applied pharmacology,* 99 (2), 314-22.

Batschelet, E., Brand, L., and Steiner, A. (1979), 'On the kinetics of lead in the human body', *Journal of mathematical biology,* 8 (1), 15-23.

Bernard, S. R. (1977), 'Dosimetric data and metabolic model for lead', *Health physics,* 32 (1), 44-6.

Bert, J. L., van Dusen, L. J., and Grace, J. R. (1989), 'A generalized model for the prediction of lead body burdens', *Environmental research,* 48 (1), 117-27.

Blake, K. C. (1976), 'Absorption of 203Pb from gastrointestinal tract of man', *Environmental Research,* 11 (1), 1-4.

Booker, D. V., et al. (1969), 'Uptake of radioactive lead following inhalation and injection', *The British journal of radiology,* 42 (498), 457-66.

Brito, J. A., et al. (2001), 'Longitudinal changes in bone lead concentration: implications for modelling of human bone lead metabolism', *J Environ Monit,* 3, 343-51.

Brito, J. A. , et al. (2005), 'Grid search: an innovative method for the estimation of the rates of lead exchange between body compartments', *J Environ Monit,* 7, 241-47.

Brown, J. S., Wilson, W. E., and Grant, L. D. (2005), 'Dosimetric comparisons of particle deposition and retention in rats and humans', *Inhalation toxicology,* 17 (7-8), 355-85.

Cal OSHA (2007a), 'Cal/OSHA General Industry Safety Orders, Lead', (Title 8 California Code of Regulations Section 5198). California Division of Occupational Safety and Health (Cal/OSHA).

--- (2007b), 'Cal/OSHA Construction Safety Orders, Lead', (Title 8 California Code of Regulations Section 1532.1).

Castellino, N., Castellino, P. , and Sannolo, N. (1995), *Inorganic Lead Exposure: Metabolism and Intoxication* (CRC Press Inc.) 516.

CDC (2009), 'National Health and Nutrition Examination Survey 2007-2008', Centers for Disease Control (CDC).

CDPH (2009), 'Medical Guidelines for the Lead-exposed Worker', California Department of Public Health (CDPH) <www.cdph.ca.gov/programs/olppp/Documents/medgdln.pdf>.

Chamberlain, A. C. (1985), 'Prediction of response of blood lead to airborne and dietary lead from volunteer experiments with lead isotopes', *Proceedings of the Royal Society of London. Series B, Containing papers of a Biological character. Royal Society,* 224 (1235), 149-82.

Chamberlain, A. C., et al. (1978), *Investigations into lead from motor vehicles* (AERE-R 9198; Oxon, UK: Harwell).

Chavalitnitikul, C., Levin, L., and Chen, L. C. (1984), 'Study and models of total lead exposures of battery workers', *Am Ind Hyg Assoc J,* 45 (12), 802-8.

Christoffersson, J. O., et al. (1986), 'Decrease of skeletal lead levels in man after end of occupational exposure', *Archives of environmental health,* 41 (5), 312-8.

Cooper, W.C., et al. (1973), ‘Laboratory studies of workers in lead smelting and refining’. In: Environmental health aspects of lead: proceedings of an international symposium of the Commission of the European Communities and the USEPA held in Amsterdam, October 2-6, 1972. Luxembourg: Commision of the European Comunities, 517-530.

deSilva, P. E. (1981). ‘Determination of lead in plasma and studies on its relationship to lead in erythrocytes’, Br J Ind Med 38(3): 209-217.

Dinman, B.D. (1991), 'The mode of absorption, distribution, and elimination of toxic materials', *Patty's Industrial Hygiene and Toxicology Part A*, 205-39.

Flanagan, P. R., Chamberlain, M. J., and Valberg, L. S. (1982), 'The relationship between iron and lead absorption in humans', *The American journal of clinical nutrition,* 36 (5), 823-9.

Fleming, D. E., et al. (1999), 'The O'Flaherty model of lead kinetics: an evaluation using data from a lead smelter population', *Toxicol Appl Pharmacol,* 161 (1), 100-9.

Fleming, D. E., et al. (1997), 'Accumulated body burden and endogenous release of lead in employees of a lead smelter', *Environ Health Perspect,* 105 (2), 224-33.

Fleming, D. E., et al. (1998), 'Effect of the delta-aminolevulinate dehydratase polymorphism on the accumulation of lead in bone and blood in lead smelter workers', *Environ Res,* 77 (1), 49-61.

Froines, J. R., et al. (1986), 'Effect of aerosol size on the blood lead distribution of industrial workers', *Am J Ind Med,* 9 (3), 227-37.

Froines, J. R. , et al. (1995), 'Prediction of Blood Lead Levels in Occupationally Exposed Workers using Toxicokinetic Modelling and Empirically-Dreived Size Distribution Data: Regulatory Implications', *Occupational Hygiene,* 1, 279-92.

GetData Graph Digitizer (version 2.24) accessed from http://getdata-graph-digitizer.com/

Griffin, S., et al. (1999), 'Calculating the interindividual geometric standard deviation for use in the integrated exposure uptake biokinetic model for lead in children', *Environ Health Perspect,* 107 (6), 481-7.

Griffin, T.B., et al. (1975), 'Clinical studies on men continuously exposed to airborne particulate lead', in Griffin T.B. Knelson J.H. (ed.), *Lead* (New York: Academic Press), 221-40.

Gross, S. B., et al. (1975). ‘Lead in human tissues’, *Toxicol Appl Pharmacol* 32(3): 638-651.

Gross, S. B. (1979), 'Oral and inhalation exposures to lead in human subjects (Kehoe Balance Experiments). ', *Final Report* (New York: Lead Industries Association Inc.).

--- (1981), 'Human oral and inhalation exposures to lead: summary of Kehoe balance experiments', *Journal of toxicology and environmental health,* 8 (3), 333-77.

Hammond, P. B., O'Flaherty, E. J., and Gartside, P. S. (1981), 'The impact of air-lead on blood-lead in man--a critique of the recent literature', *Food Cosmet Toxicol,* 19 (5), 631-8.

Hirata, M., et al. (1995), ‘Correlation between lead in plasma and other indicators of lead exposure among lead-exposed workers’, *Int Arch Occup Environ Health* 68(1): 58-63.

Harrison, G. E., et al. (1969), 'Effect of alginate on the absorption of lead in man', *Nature,* 224 (5224), 1115-6.

Hattis, D. (1981), 'Dynamics of Medical Removal Protection for Lead - A Reappraisal', in N.A. Ashford, Principal Investigator (ed.), (Cambridge, Massachusetts: Massachusetts Institue of Technology).

Heard, M. J. and Chamberlain, A. C. (1982), 'Effect of minerals and food on uptake of lead from the gastrointestinal tract in humans', *Human toxicology,* 1 (4), 411-5.

Hinds, W. C. (1982), *Aerosol Technology Properties, Behavior, and Measurement of Airborne Particles* (New York: John Wiley & Sons).

Hodgkins, D. G., et al. (1991a), 'Influence of high past lead-in-air exposures on the lead-in-blood levels of lead-acid battery workers with continuing exposure', *J Occup Med,* 33 (7), 797-803.

Hodgkins, D. G., et al. (1991b), 'The effect of airborne lead particle size on worker blood-lead levels: an empirical study of battery workers', *J Occup Med,* 33 (12), 1265-73.

Hodgkins, D. G., et al. (1992), 'A longitudinal study of the relation of lead in blood to lead in air concentrations among battery workers', *British journal of industrial medicine,* 49 (4), 241-8.

Holgate ST (1999) 'Air Pollution and Health', Academic Press, Apr 21, 1999- 1065 pages; edited by Stephen T. Holgate, Hillel S. Koren, Jonathan M. Samet, Robert L. Maynard

Hursh, J. B. and Suomela, J. (1968), 'Absorption of 212Pb from the gastrointestinal tract of man', *Acta radiologica: therapy, physics, biology,* 7 (2), 108-20.

Hursh, J. B., et al. (1969), 'Fate of 212Pb inhaled by human subjects', *Health physics,* 16 (3), 257-67.

ICRP (1994), *Human Respiratory Tract Model for Radiological Protection*, ed. H. Smith (1st edn., Annals of the ICRP, 66; Oxfordshire: Pergamon) 482, International Commission on Radiologic Protection (ICRP).

--- (2002), 'Basic anatomical and physiological data for use in radiological protection: Reference values', (ICRP Report).

Inskip, M. J. and Hutton, M. (1987), 'Lead-based paint in dwellings: the potential for contamination of the home environment during renovation', *Environ Geochemistry and Health,* 9 (3-4), 86-92.

Jacko, R. B. and Overmyer, R.C. (1979), 'Characterization of particulates and lead in a brass foundry using a close capture exhaust system', *Proceedings of the symposium on occupational health hazard control technology in the foundry and secondary non-ferrous smelting industries* (Chicago, Illinois: U.S. Department of Health and Human Services).

James, H. M., Hilburn, M. E., and Blair, J. A. (1985), 'Effects of meals and meal times on uptake of lead from the gastrointestinal tract in humans', *Human toxicology,* 4 (4), 401-7.

Kim, R., et al. (1996), 'A longitudinal study of low-level lead exposure and impairment of renal function. The Normative Aging Study', *JAMA : the journal of the American Medical Association,* 275 (15), 1177-81.

Kononen, D.W., Kintner, H.J., and K.R., Bivol (1989), 'Air lead exposures and blood lead levels within a large automobile manufacturing workforce, 1980-1985', *Arch. Environ. Health,* 44, 244-51.

Lee, B. K. (1982), ‘Occupational lead exposure of storage battery workers in Korea." Br J Ind Med 39(3): 283-289.

Leggett, R. W. (1993), 'An age-specific kinetic model of lead metabolism in humans', *Environ Health Perspect,* 101 (7), 598-616.

Leggett, R. W., Eckerman, K. F., and Williams, L. R. (1982), 'Strontium-90 in bone: a case study in age-dependent dosimetric modeling', *Health physics,* 43 (3), 307-22.

Liu, W.V., Froines, J.R. , and Hinds, W.C. (1996), 'Particle Size Distribution of Lead Aerosol in a Brass Foundry and a Battery Manufacturing Plant', *Occupational Hygiene,* 3, 213-28.

Liu, W.V. , Landaw, E.M. , and Froines, J.R. (1995), 'Comparison of the Dynamic Behavior of Compartmental Models for Lead Distribution in the Human Body', *Occupational Hygiene,* 1, 293-304.

Lynam, D. R. and Nelson, K.W. (1981), 'Predicting Return to Work After Medical Removal Required by Health Standards', *Mining Congress Journal,* (August), 41-44.

Manton, W. I. and Malloy, C. R. (1983), 'Distribution of lead in body fluids after ingestion of soft solder', *British journal of industrial medicine,* 40 (1), 51-7.

Manton, W. I. and Cook, J. D. (1984), 'High accuracy (stable isotope dilution) measurements of lead in serum and cerebrospinal fluid', *British journal of industrial medicine,* 41 (3), 313-9.

Marcus, A. H. (1985a), 'Multicompartment kinetic model for lead. III. Lead in blood plasma and erythrocytes', *Environmental research,* 36 (2), 473-89.

--- (1985b), 'Multicompartment kinetic models for lead. II. Linear kinetics and variable absorption in humans without excessive lead exposures', *Environmental research,* 36 (2), 459-72.

--- (1985c), 'Multicompartment kinetic models for lead. I. Bone diffusion models for long-term retention', *Environmental research,* 36 (2), 441-58.

MATLAB (2012) version 8.0.0.783, Natick, Massachusetts: The MathWorks Inc.(Matrix Laboratory).

Meridian Research Inc. (1992), 'Quantitative Assessment of the Risks Associated with Exposure to Lead in the Construction Industry: Selected Toxicological Endpoints', *Peer Review Draft Report* (Maryland: Meridian Research Inc.).

Microsoft. (2010). Microsoft Excel [computer software]. Redmond, Washington: Microsoft.

Monosson, E. (2011) NLM (Content Source);Emily Monosson (Topic Editor) "Absorption of toxicants". In: Encyclopedia of Earth. Eds. Cutler J. Cleveland (Washington, D.C.: Environmental Information Coalition, National Council for Science and the Environment). [First published in the Encyclopedia of Earth February 28, 2008;

Last revised Date October 4, 2011; Retrieved October 26, 2012 <http://www.eoearth.org/article/Absorption_of_toxicants

NTP (2011) 'Lead and lead compounds Report on Carcinogens', Twelfth Edition, National Toxicology program, department of health and human services http://ntp.niehs.nih.gov/go/roc12

Nie, H., et al. (2005), 'The study of age influence on human bone lead metabolism by using a simplified model and X-ray fluorescence data', *Journal of environmental monitoring : JEM,* 7 (11), 1069-73.

OEHHA (2012a), **'**Air Toxics Hot Spots Program Risk Assessment Guidelines: Technical Support Document for Exposure Assessment and Stochastic Analysis' available at: **http://www.oehha.ca.gov,** Office of Environmental Health Hazard Assessment (OEHHA).

OEHHA (2012b) 'Nickel Reference Exposure Levels', available at: http://www.oehha.ca.gov/air/chronic_rels/pdf/032312NiREL_Final.pdf

O'Flaherty, E. J., P.B., Hammond, and S.I., Lerner (1982), 'Dependence of apparent blood lead half-life on the length of previous lead exposure in humans', *Fundam Appl Toxicol,* 2, 49-54.

O'Flaherty, E. J. (1986), 'The rate of decline of blood lead in lead industry workers during medical removal: the effect of job tenure', *Fundamental and applied toxicology : official journal of the Society of Toxicology,* 6 (2), 372-80.

--- (1991), 'Physiologically based models for bone-seeking elements. II. Kinetics of lead disposition in rats', *Toxicol Appl Pharmacol,* 111 (2), 313-31.

--- (1993), 'Physiologically based models for bone-seeking elements. IV. Kinetics of lead disposition in humans', *Toxicol Appl Pharmacol,* 118 (1), 16-29.

--- (1995), 'Physiologically based models for bone-seeking elements. V. Lead absorption and disposition in childhood', *Toxicol Appl Pharmacol,* 131 (2), 297-308.

--- (2000), 'Modeling normal aging bone loss, with consideration of bone loss in osteoporosis', *Toxicological sciences : an official journal of the Society of Toxicology,* 55 (1), 171-88.

O'Flaherty, E. J., et al. (1996), 'Plasma and blood lead concentrations, lead absorption, and lead excretion in nonhuman primates', *Toxicol Appl Pharmacol,* 138 (1), 121-130.

O'Flaherty, E. J., et al. (1998), 'Evaluation and modification of a physiologically based model of lead kinetics using data from a sequential isotope study in cynomolgus monkeys', *Toxicol Appl Pharmacol,* 149 (1), 1-16.

OSHA. (1978), 'Occupational Exposure to Lead: Attachments to the Preamble for the Final Standard', in Occupational Safety and Health Administration (OSHA) (ed.), (43: Federal Register), 54353*509.

Park, D. U. and Paik, N. W. (2002), 'Effect on blood lead of airborne lead particles characterized by size', *The Annals of occupational hygiene,* 46 (2), 237-43.

Popovic, M., et al. (2005), 'Impact of occupational exposure on lead levels in women', *Environ Health Perspect,* 113 (4), 478-84.

Pounds, J. G. and Leggett, R. W. (1998), 'The ICRP age-specific biokinetic model for lead: validations, empirical comparisons, and explorations', *Environ Health Perspect,* 106 Suppl 6, 1505-11.

Rabinowitz, M. B., Kopple, J. D., and Wetherill, G. W. (1980), 'Effect of food intake and fasting on gastrointestinal lead absorption in humans', *The American journal of clinical nutrition,* 33 (8), 1784-8.

Rabinowitz, M.B. , Wetherill, G.W. , and J.D., Kopple (1976), 'Kinetic Analysis of Lead Metabolism in Healthy Humans', *Journal of Clinical Investigations,* 58, 260-70.

Raghavan, S.R. , Culver, B.D. , and Gonick, H.C. (1980), 'Erythrocyte lead-binding Protein after Occupational Exposure. !. Relationship to lead toxicity', *Environmental Research,* 22, 264-70.

RIVM. (2002), 'Multiple Path Particle Dosimetry Model (MPPD v 1.0): Multiple Path Particle Dosimetry Model (MPPD v 1.0): A Model for Human and Rat Airway Particle Dosimetry.', (Bilthoven, The Netherlands: National Institute for Public Health and the Environment [RIVM]).

Rodrigues, E. G., et al. (2010), 'Personal exposure, behavior, and work site conditions as determinants of blood lead among bridge painters', *Journal of occupational and environmental hygiene,* 7 (2), 80-7.

SCAQMD. (2008), 'Multiple Air Toxics Exposure Study in the South Coast Air Basin MATES III Final Report'. South Coast Air Quality Management District (SCAQMD).

Schober, S. E., et al. (2006), 'Blood lead levels and death from all causes, cardiovascular disease, and cancer: Results from the NHANES III Mortality Study', *Environmental Health Perspectives,* 114 (10), 1538-41.

Schroeder, H.A., and Tipton, I.H., (1968), ‘The human body burden of lead’, Arch Environ Health 17: 965-978.

Schutz, A., et al. (1987), 'Kinetics of lead in blood after the end of occupational exposure', *Scand J Work Environ Health,* 13 (3), 221-31.

Schwartz, B. S., et al. (2000), 'Associations of blood lead, dimercaptosuccinic acid-chelatable lead, and tibia lead with polymorphisms in the vitamin D receptor and [delta]-aminolevulinic acid dehydratase genes', *Environ Health Perspect,* 108 (10), 949-54.

Skerfving, S. , et al. (1987), 'Biological Monitoring, by in vivo XRF measurements, of occupational exposure to lead, calcium, and mercury', *Biol Trace Elem Res* 13, 241-51.

Smith, J. R., et al. (2011). "An experimental study of clearance of inhaled particles from the human nose." Exp Lung Res **37**(2): 109-129.

Snee, R. D. (1981), 'Evaluation of studies of the relationship between blood lead and air lead', *Int Arch Occup Environ Health,* 48 (3), 219-42.

Snee, R. D. (1982), 'Models for the relationship between blood lead and air lead', *Int Arch Occup Environ Health,* 50 (4), 303-319.

Spear, T. M., et al. (1998a), 'Chemical speciation of lead dust associated with primary lead smelting', *Environ Health Perspect,* 106 (9), 565-71.

Spear, T. M., et al. (1998b), 'Assessment of particle size distributions of health-relevant aerosol exposures of primary lead smelter workers', *The Annals of occupational hygiene,* 42 (2), 73-80.

Stellman (1998) Encyclopaedia of Occupational Health and Safety vol 1 by Jeanne Mager Stellman International Labour Organization.

Sussell, A., Mickelsen, R.L., and Rubin, C. (1992), 'Health Hazard Evaluation Report: M & J Painting Company Covington, Kentucky', in NIOSH (ed.), (Health Hazard Evaluation Report: US Department of Health and Human Services Public Health Service Centers for Disease Control National Institute for Occupational Safety and Health).

Tipton, I. H. and M. J. Cook (1963), ‘Trace elements in human tissue. II. Adult subjects from the United States’, *Health Phys* 9: 103-145.

Tsai, C. J., Shih, T. S., and Sheu, R. N. (1997), 'Characteristics of lead aerosols in different work environments', *American Industrial Hygiene Association journal,* 58 (9), 650-6.

U.S. EPA. (1991), 'Risk Assessment Guidance for Superfund Volume 1 Human Health Evaluation Manual Supplemental Guidance: Standard Default Exposure Factors', in OSWER (ed.), (directive 9825.6-03). United States 'Environmental Protection Agency (U.S. EPA).

--- (1997), 'Exposure Factors Handbook', (1, General Factors; Washington D.C.: U.S. Environmental Protection Agency).

--- (2003), 'The Adult Lead Methodology (ALM)', in OSWER (ed.), (Dir #9285.7-54 December 1996 (January 2003): U.S. Environmental Protection Agency).

--- (2005), 'All Ages Lead Model external review draft'.

--- (2009), 'Update of The Adult Lead Methodology's Default Baseline Blood Lead Concentration and Geometric Standard Deviation Parameter'.

U.S. EPA, SAB. (2011), ‘Review of EPA's Approach for Developing Lead Dust Hazard Standards for Residences (November 2011 Draft) and Approach for Developing Lead Dust Hazard Standards for Public and Commercial Buildings'. Environmental Protection Agency Science Advisory Board. (EPA SAB).

Virji, M. A., Woskie, S. R., and Pepper, L. D. (2009),'Task-based lead exposures and work site characteristics of bridge surface preparation and painting contractors', *J Occup Environ Hyg,* 6 (2), 99-112.

Vork, K.L. (2003), 'Development of an Occupational Air Contaminant Exposure Monitoring and Control Strategy: with Application to Lead Exposure during Bridgework', Dissertation (University of California Berkeley).

Wang, Y. L., et al. (1985). ‘Effects of occupational lead exposure’*, Scand J Work Environ Health,* 11 Suppl 4: 20-25.

White, P. D., et al. (1998), 'The conceptual structure of the integrated exposure uptake biokinetic model for lead in children', *Environ Health Perspect,* 106 Suppl 6, 1513-30.

Williams, M. K., King, E., and Walford, J. (1969), 'An investigation of lead absorption in an electric accumulator factory with the use of personal samplers', *British journal of industrial medicine,* 26 (3), 202-16.

Yeh, H. C. and Schum, G. M. (1980), 'Models of human lung airways and their application to inhaled particle deposition', *Bulletin of mathematical biology,* 42 (3), 461-80.